VERIFICATION OF TRANSLATION

I, Tetsuya KIMIZUKA of c/o Yamanouchi Pharmaceutical Co., Ltd., Patent Dept., 17-1, Hasune 3-chome, Itabashi-ku, Tokyo 174-8612 Japan, declare as follows:

1. That I am well acquainted with both the English and Japanese languages, and

2. That the attached document is a true and correct translation made by me to the best of my knowledge and belief of:

the specification of Japanese Patent Application numbered
Patent Application No. 2002-10447

Signature of translator

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[Article Name] Specification 1

[Article Name]	Abstract	1
[Necessity of Proof]	YES	

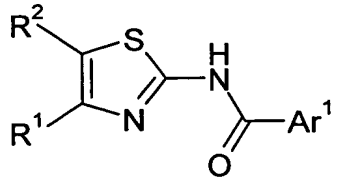
[Designation of the Document] Specification

[Title of the invention] 2-ACYLAMINOTHIAZOLE DERIVATIVE AND SALT THEREOF

[Claims]

[Claim 1] A pharmaceutical composition for increasing platelets comprising a 2-acylaminothiazole derivative represented by the following general Formula (I) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



(I)

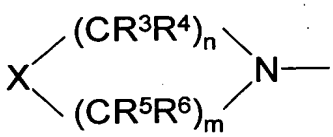
[wherein symbols have the following meanings.

Ar^1: optionally substituted aryl, monocyclic aromatic heterocycle, or bicyclic condensed heterocycle,

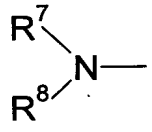
R^1: optionally substituted aryl, or pyridyl,

R^2: a group represented by the following general Formula (II) or (III):

[Chemical Formula 2]



(II)



(III)

n: an integer of 1 to 3,

m: an integer of 1 to 2,

X: O, S, or a group represented by $N(R^9)$, or $C(R^{10})(R^{11})$,

R^3, R^4, R^5, R^6, R^9, R^{10} and R^{11}: which may be identical or different,

H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted aralkyl; optionally substituted aromatic heterocycle; optionally substituted heteroarylalkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl or –O-aryl, and cycloalkyl; -NHCO-lower alkyl; or, oxo,

Wherein, in case n or m is an integer of 2 or more, CR^3R^4 and CR^5R^6 may be identical or different.

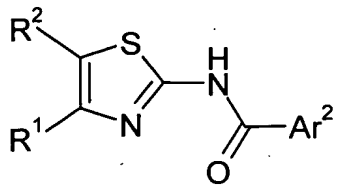
R^7 and R^8: which may be identical or different, -H, optionally substituted lower alkyl, optionally substituted cycloalkyl, or optionally substituted nonaromatic heterocycle.]

[Claim 2] The pharmaceutical composition according to Claim 1, wherein the pharmaceutical composition is used as a therapeutic agent for thrombocytopenia.

[Claim 3] The pharmaceutical composition according to Claim 1, wherein the pharmaceutical composition is a c-Mpl ligand.

[Claim 4] A 2-acylaminothiazole derivative represented by the following general Formula (IV) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 3]



(IV)

[wherein symbols have the following meanings.

Ar^2: optionally substituted aryl or monocyclic aromatic heterocycle, optionally substituted bicyclic condensed heterocycle, with the proviso that indol is excluded,

R^1: optionally substituted aryl or pyridyl,

R^2: a group represented by the general Formula (II) or (III) in Claim 1.]

[Claim 5] The compound or pharmaceutically acceptable salt thereof according to Claim 4, wherein R^1 is optionally substituted phenyl, and R^2 is a group represented by the general Formula (II), (wherein n is 2, m is 2, and X is a group represented by $N(R^9)$, $C(R^{10})(R^{11})$).

[Claim 6] A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof according to Claim 4 or Claim 5 as an active ingredient.

[Detailed description of the invention]

[0001]

[Field of the invention]

The present invention relates to a novel 2-acylaminothiazole derivative or a salt thereof, which is useful as a medicament particularly in the treatment of thrombocytopenia, and a medicament comprising the compound as an active ingredient.

[0002]

[Description of the Related Art]

A platelet is anuclear blood cell playing an important role in physiological hemostasis and pathological thrombosis, and is continuously produced from megakaryocytes in a living body. The platelet is originated from pluripotent stem cells like other blood cells. Specifically, the pluripotent stem cell becomes megakaryocytic progenitor cell, from which megakaryoblasts, promegakaryocytes and megakaryocytes are formed. During the maturation of the megakaryocyte, premature megakaryocyte carries out only DNA synthesis without involving a cell division to become a polyploid. Thereafter, cytoplasm begins to mature to form a platelet separation membrane, and platelet is released by cytoplasm fragmentation.

In addition, since platelet decrease due to various hematopoietic dysfunctions in aplastic anemia, myelodysplastic syndrome, or chemotherapy or radiotherapy for malignant tumor and the like causes serious symptoms such as hemorrhage tendency, there have been many attempts for developing various technologies for increasing platelets for the purpose of treating them. At present, although a platelet transfusion is a powerful means for treating thrombocytepenia, sufficient amount of platelet cannot be provided, and it is difficult to sufficiently improve thrombocytepenia because of short life span of transfused platelet and the like. And, a platelet transfusion involves problems including viral infection, production of alloantibodies, and Graft Versus Host Disease (GVHD) and the like. Thus, there is a demand for the development of a medicament for mitigating hematopoietic suppression caused by various conditions or therapies thereby promoting the recovery of platelet number.

[0003]

Meanwhile, it was reported that thrombopoietin (herein after referred to as 'TPO'), which is a c-Mpl ligand playing an important role in differentiation into megakaryocyte, was cloned, and that it stimulates differentiation and proliferation of megakaryocyte to promote production of platelet (Kaushansky K. et. al., Nature, 369, 568-571, 1994: Non Patent Document 1). Clinical tests on TPO as platelet increasing agent have already been carried out, and its availability and admissibility in human have been confirmed. However, because a neutralizing antibody was confirmed in a clinic test of PEG-rHuMGDF, a kind of TPO (163 N-terminal amino acids of native TPO modified with polyethyleneglycol) (Vadhan-Raj S, Semin Hematol., 37(suppl. 4), 28-34, 2000), there is a concern about immunogenicity of TPO. And, because TPO is a protein, it is decomposed in a digestive tract, and thus is not practical for an agent for oral administration. For the same reason, it is considered that low molecular peptide is also not practical for an agent for oral administration. Under these circumstances, the development of nonpeptide c-Mpl ligand, which has low immunogenicity and can be orally administrated, for the purpose of treatment of thrombocytepenia, is under progress.

[0004]

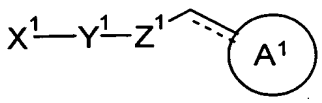
As such compounds, benzazepine derivatives are disclosed in Japanese Laid-Open Patent Publication No. Hei 11-152276, acylhydrazone derivatives in WO 99/11262, diazonaphthalene derivatives in WO 00/35446, pyrrolocarbazole derivatives in WO 98/09967, pyrrolophenanthridine derivative in Japanese Laid-Open Patent Publication No. Hei 10-212289,

and pyrrolophthalimide derivatives in Japanese Laid-Open Patent Publication No. Hei 2000-44562.

[0005]

And, it is described in WO 01/07423 that a compound represented by the following general Formula (VII) has an activity of increasing platelet:

[Chemical Formula 4]



(VII)

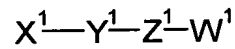
(wherein symbols are as defined in the above publication)

And, the above publication describes a compound wherein X^1 is optionally substituted thiazole, and Y^1 comprises –NHCO-. However, Ar^1 or Ar^2 of the compound of the present invention is not substituted with a substituent group having A^1 group such as thiazolyl group as in the above publication. And, the above publication does not mention in the Examples and the others a compound wherein 5 position of thiazole is directly substituted with a nitrogen atom.

[0006]

And, it is described in WO 01/53267 that a compound represented by the following general Formula (VIII) has an activity of increasing platelet:

[Chemical Formula 5]



(VIII)

(wherein symbols are as defined in the publication)

The above publication describes a compound wherein X^1 is optionally substituted thiazole, and Y^1 comprises –NHCO-. However, Ar of the compound of the present invention is not substituted with a substituent

group having W^1 group. And, the above publication does not mention in the Examples and the others a compound wherein 5 position of thiazole is directly substituted with a nitrogen atom.

[0007]

And, in addition to the WO01/07423 and WO01/53267, it is described in Japanese Patent Publication No. 3199451 that 2-acylaminothiazole compound has the effects of cholecystokinin and gastrin receptor agonist, and it is described in Chemical and Pharmaceutical Bulletin, 25, 9, 2292-2299, 1977 that 2-acylaminothiazole compound has anti-inflammatory effects. However, there is no description about platelet increasing activity.

[0008]

[Object of the invention]

Under these circumstances, there is a demand for the development of nonpeptide c-Mpl ligand that has low immunogenicity and can be orally administrated, for the purpose of treatment of thrombocytopenia.

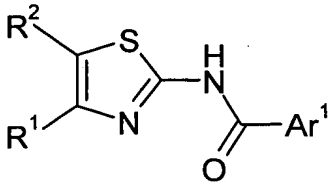
[0009]

[Means to achieve the object]

The inventors, as results of assiduous studies on compounds having activities of increasing platelets, discovered that novel 2-acylaminothiazole derivatives have excellent platelet increasing effects, and completed the present invention.

The present invention relates to a pharmaceutical composition for increasing platelets comprising a 2-acylaminothiazole derivative represented by the following general Formula (I) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 6]



(I)

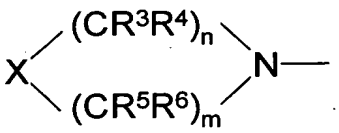
[wherein symbols have the following meanings.

Ar^1: optionally substituted aryl, monocyclic aromatic heterocycle, or bicyclic condensed heterocycle,

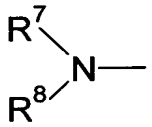
R^1: optionally substituted aryl or pyridyl,

R^2: a group represented by the following general Formula (II) or (III):

[Chemical Formula 7]



(II)



(III)

n: an integer of 1 to 3,

m: an integer of 1 to 2,

X: O, S, or a group represented by $N(R^9)$, or $C(R^{10})(R^{11})$,

R^3, R^4, R^5, R^6, R^9, R^{10} and R^{11}: which may be identical or different, -H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted aralkyl; optionally substituted aromatic heterocycle; optionally substituted heteroarylalkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more

groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl or –O-aryl, and cycloalkyl; -NHCO-lower alkyl; or, oxo,

wherein, in case n or m is an integer of 2 or more, CR^3R^4 and CR^5R^6 may be identical or different.

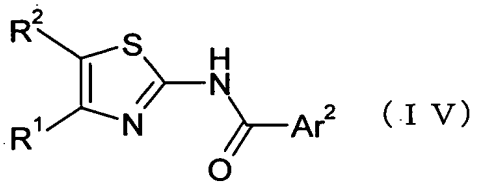
R^7 and R^8: which may be identical or different, -H, optionally substituted lower alkyl, optionally substituted cycloalkyl, or optionally substituted nonaromatic heterocycle.]

The present invention also relates to a platelet increasing agent represented by the general Formula (I) that is a therapeutic agent for thrombocytopenia, and a c-Mpl ligand.

[0010]

The present invention also relates to a 2-acylaminothiazole derivative represented by the general Formula (IV) or a pharmaceutically acceptable salt thereof.

[Chemical Formula 8]



(IV)

[wherein symbols have the following meanings.

Ar^2: optionally substituted aryl or monocyclic aromatic heterocycle, optionally substituted bicyclic condensed heterocycle, with the proviso that indol is excluded,

R^1: optionally substituted aryl or pyridyl,

R^2: a group represented by the general Formula (II) or (III) in Claim

1.]

Preferred is a 2-acylaminothiazole derivative represented by the general Formula (IV) or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted phenyl, and R^2 is a group represented by the general Formula (II), (wherein n is 2, m is 2, and X is a group represented by $N(R^9)$, $C(R^{10})(R^{11})$).

The present invention also relates to a pharmaceutical composition comprising the 2-acylaminothiazole derivative represented by the general Formula (IV) or a pharmaceutically acceptable salt thereof, or the 2-acylaminothiazole derivative represented by the general Formula (IV) or a pharmaceutically acceptable salt thereof wherein R^1 is optionally substituted thienyl, and R^2 is a group represented by the general Formula (II), (wherein n is 2, m is 2, and X is a group represented by $N(R^9)$, $C(R^{10})(R^{11})$), as an active ingredient.

[0011]

[Preferred embodiment of the invention]

The following describes the compound of the invention in detail.

In the definition of the general formula of the present invention, the term "lower" means a straight or branched carbon chain having from 1 to 6 carbon atoms, unless otherwise indicated.

Thus, the "lower alkyl" means alkyl having 1 to 6 carbon atoms, and its examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, and the like, of which those having 1 to 3 carbon atoms such as methyl, ethyl, propyl, and isopropyl are preferred.

The 'lower alkenyl' means alkenyl having 2 to 6 carbon atoms, and its examples include ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like, of which those having 2 to 3 carbon atoms such as ethenyl, 1-propenyl, 2-propenyl and 3-propenyl are preferred.

The 'lower alkylidene' means alkylidene having 1 to 6 carbon atoms, and its examples include methylidene, ethylidene, propylidene, butylidene, pentylidene, hexylidene, and the like, of which those having 1 to 3 carbon atoms such as methylidene, ethylidene, 1-propylidene and 2-propylidene are preferred.

The 'lower alkylene' means a divalent group of alkyl having 1 to 6 carbon atoms, of which those having 1 to 4 carbon atoms such as methylene, ethylene, trimethylene, methylethylene, tetramethylene, dimethylmethylene and dimethylethylene are preferred.

[0012]

The 'cycloalkyl' means a carbon ring having 3 to 8 carbon atoms. Its examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, and the like.

The 'aryl' means a mono- to tri-cyclic aromatic ring having 6 to 14 carbon atoms, of which phenyl and naphthyl are preferred, and phenyl is more preferred.

The 'aralkyl' means the 'lower alkyl' substituted with the 'aryl', and its examples include benzyl, 1-phenethyl, 2-phenethyl, naphthylmethyl, 1-naphthylethyl, 2-naphthylethyl and the like.

[0013]

The 'monocyclic aromatic heterocycle' means a monovalent group of

five- to six-membered aromatic heterocycle, which may comprise nitrogen, oxygen or sulfur atom, and its examples include thienyl, furyl, pyrrolyl, thiazolyl, oxazoylyl, imidazolyl, isothiazolyl, isoxazolyl, pyrazolyl, thiadiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and the like.

The 'aromatic heterocycle' means a monovalent group of aromatic heterocycle, a hetero ring which may have 1 to 4 hetero atoms, which may be identical or different, selected from the group consisting of nitrogen, oxygen and sulfur, and its examples include, in addition to the 'monocyclic aromatic heterocycle', indolyl, isoindolyl, indolizinyl, indazolyl, quinolyl, isoquinolyl, quinolidinyl, phthalazinyl, naphthylidinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothienyl, benzothiazolyl, oxazolopyridyl, thiazolopyridyl and the like.

[0014]

The 'bicyclic condensed heterocycle' means a monovalent group of an aromatic heterocycle condensed with aryl or monocyclic aromatic heterocycle, or its partially hydrogenated ring, which may comprise nitrogen, oxygen or sulfur atom, and its example include indolyl, isoindolyl, indolizinyl, indazolyl, quinolyl, isoquinolyl, quinolidinyl, phthalazinyl, naphthylidinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothienyl, benzothiazolyl, oxazolopyridyl, thiazolopyridyl, indolinyl, isoindolinyl, 1,2-dihydroquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 1,4-dihydro-2H-3,1-benzoxazinyl, chromanyl, isochromanyl, benzoxolanyl,

benzodioxolanyl, benzodioxanyl and the like.

[0015]

The 'heteroaryl alkyl' means the 'lower alkyl' substituted with the 'aromatic heterocycle', and its examples include thienylmethyl, furylmethyl, pyridylmethyl, thiazolylmethyl, oxazolylmethyl, imidazolylmethyl, thienylethyl, furylethyl, pyridylethyl and the like.

The 'non-aromatic heterocycle' means a monovalent group of nonaromatic heterocycle, which may have one or more hetero atoms, which are identical or different, selected from the group consisting of nitrogen, oxygen and sulfur, and its examples include azetidinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, azepinyl, piperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, and the like.

[0016]

The 'halogen' includes fluorine, chlorine, bromine, and iodine atoms.

The 'ligand' means a low molecular weight substance binding to an enzyme, receptor, protein, and the like, and includes agonist and antagonist, of which agonist is preferred.

[0017]

As substituent groups that can be used for the term "optionally substituted" or "which may be substituted", those commonly used as substituent groups for each group can be used, and each group may have one or more substituent groups.

[0018]

As the substituent groups that can be used for the "optionally substituted aryl, monocyclic aromatic heterocycle, or bicyclic condensed

heterocycle" in the definition of Ar^1 and Ar^2, lower alkyl which may be substituted with one or more halogen atoms, halogen, oxo and a group represented by the general Formula (X) can be exemplified.

[Chemical Formula 9]

—B—C—A (X)

[wherein symbols have the following meanings.

-B-: -O-, -NH-, -N(R^{12})-, or a single bond

R^{12}: lower alkyl which may be substituted with one or more groups selected from the group consisting of halogen, -OH, -O-lower alkyl and cyano,

-C-: lower alkylene which may be substituted with one or more groups selected from the group consisting of halogen, -OH, -O-lower alkyl and oxo, or a single bond,

-A: a group selected from the following (a) to (e)

(a) halogen, -OH, -O-lower alkyl, -CO-lower alkyl, -COOH, -COO-lower alkyl, cyano, -$NHCONH_2$ or –$NHSO_2NH_2$.

(b) carbamoyl or amino, each of which may be substituted with one or two groups selected from the group consisting of lower alkyl and cycloalkyl.

(c) –NHCO-lower alkyl, -NHCOO-lower alkyl or –$NHSO_2$-lower alkyl, each of which may be substituted with –O-lower alkyl.

(d) –O-aryl which may be substituted with one or more groups selected from the group consisting of –OH, -O-lower alkyl and –O-lower alkylene-O-lower alkyl.

(e) aryl, aromatic heterocycle, nonaromatic heterocycle, -O-aralkyl, or –O-heteroarylalkyl, each of which may be substituted with one or more groups described in the following.

lower alkyl which may be substituted with one or more groups selected from the group consisting of halogen, -OH and –O-lower alkyl;

-OH; -O-lower alkyl; -O-lower alkylene-O-lower alkyl;

-COOH; -COO-lower alkyl; -CO-lower alkyl;

carbamoyl; N-lower alkyl or N,N-di lower alkyl carbamoyl; N-cycloalkyl or N,N-dicycloalkylcarbamoyl; N-lower alkyl-N-cycloalkylcarbamoyl; -CO-nonaromatic heterocycle; amino; N-loweralkyl or N,N-diloweralkylamino; N-cycloalkyl or N,N-dicycloalkylamino; N-loweralkyl-N-cycloalkylamino; cyano; halogen; oxo,

with the proviso that when B is a single bond, A is –COOH, -COO-lower alkyl, optionally substituted carbamoyl, optionally substituted aryl, or optionally substituted aromatic heterocycle, C is methylene.

[0019]

In case Ar^1 and Ar^2 are aryl or pyridyl, loweralkyl, -CO-lower alkyl, -COO-lower alkyl, -OH, -O-lower alkyl, -OCO-lower alkyl and halogen are excluded from the substituent groups.

[0020]

As the substituent groups that can be used for 'optionally substituted aryl or pyridyl", "optionally substituted phenyl" in the definition of R^1, lower alkyl which may be substituted with one or more halogen atoms, -OH, -O-lower alkyl, -COOH, -COO-lower alkyl, carbamoyl or amino which may be substituted with 1 or 2 lower alkyl, cyano, nitro and halogen can be exemplified.

[0021]

As the substituent groups that can be used for 'optionally substituted

lower alkyl' in the definitions of R^3, R^4, R^5, R^6, R^7,R^8, R^9, R^{10}, and R^{11}, -OH; -O-lower alkyl; -O-aryl; -COOH; -COO-lower alkyl; carbamoyl which may be substituted with 1 or 2 groups selected from the group consisting of lower alkyl and cycloalkyl; amino which may be substituted with 1 or 2 groups selected from the group consisting of lower alkyl and cycloalkyl; cyano; halogen; oxo; nonaromatic heterocycle which may be substituted with one or more groups selected from the group consisting of lower alkyl, -O-lower alkyl, -OH and halogen can be exemplified.

[0022]

As the substituent groups that can be used for 'optionally substituted cycloalkyl', 'optionally substituted aryl', 'optionally substituted aralkyl', 'optionally substituted aromatic heterocycle', 'optionally substituted heteroarylalkyl', 'optionally substituted nonaromatic heterocycle' , 'optionally substituted thienyl' in the definitions of R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11}, lower alkyl which may be substituted with one or more halogen atoms; -OH, ;-O-lower alkyl; -O-lower alkyl-O-lower alkyl; -COOH; -COO-lower alkyl; -CO-lower alkyl; carbamoyl which may be substituted with 1 or 2 groups selected from the group consisting of lower alkyl and cycloalkyl; amino which may be substituted with 1 or 2 groups selected from the group consisting of lower alkyl and cycloalkyl; cyano; halogen; oxo; nonaromatic heterocycle which may be substituted with one or more groups selected from the group consisting of lower alkyl, -O-lower alkyl, -OH and halogen, and the like can be exemplified.

[0023]

The compound of the present invention represented by the general

Formula (I) or (IV) may comprise asymmetric carbon atoms depending on the kinds of substituent groups, and optical isomers based on the asymmetric carbon atom may exist. The compound of the present invention includes a mixture of these optical isomers or isolated one. And, tautomers may exist in the compound of the present invention, and the compound of the present invention includes these isomers as a mixture or an isolated one. As the tautomer, 2-hydroxypyridine and 2-pyridone can be exemplified.

[0024]

In addition, the compound of the present invention may form a salt, which is included in the present invention as long as pharmaceutically acceptable. Examples of the salt include addition salts with a mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethansulfonic acid, p-toluenesulfonic acid, aspartic acid, glutamic acid and the like; salts with an inorganic base such as sodium, potassium, magnesium, calcium and the like, or an organic base such as methylamine, ethylamine, ethanolamine, lysine, ornithine and the like; and ammonium salts, and the like. And, a hydrate and a solvate of the compound and its pharmaceutically acceptable salt of the present invention, and those having polymorphism are also included in the present invention. In addition, the compound of the present invention also includes a compound which is metabolized in a living body to be converted into the compound of the general Formula (I) or (IV) or its salt, so called prodrug. As groups

forming the prodrug, those described in Prog. Med., 5; 2157-2161, 1985. and Hirokawa-Shoten, 1990, "Development of medicine" Vol. 7, Molecular Design, pp 163-198 can be exemplified.

[0025]

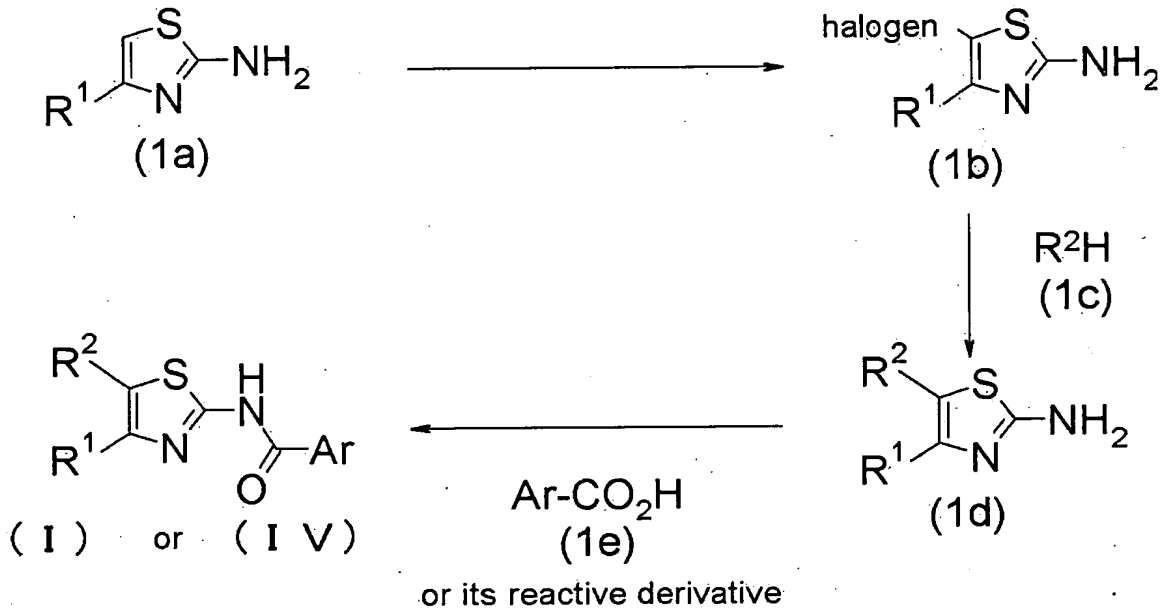
(Production Method)

The compound and its pharmaceutically acceptable salt of the present invention can be prepared by various known synthesis methods, using characteristics based on its basic backbone or the kinds of substituent groups. The following describes representative preparation methods. And, according to the kinds of functional groups, it is advantageous in some cases in terms of preparation technique to substitute a functional group with a suitable protection group, i.e., a group that can be easily converted into the functional group, in the step of raw material or intermediate. Then, if necessary, the protection group is removed to obtain a desired compound. Examples of the functional group include hydroxyl, carboxyl and amino group, and examples of the protection group include those described in "Protective Groups in Organic Synthesis ", third edition, edited by Greene and Wuts. It is preferable to suitably use them depending on reaction conditions.

[0026]

(First production method)

[Chemical Formula 10]



(wherein R^1, R^2, Ar are as defined in the foregoing)

In this method, a compound of the general Formula (I) or (IV) is prepared by the amidation of a compound (1d) or its salt with a compound (1e) or its reactive derivative by a general method, and then, if necessary, removing a protection group.

As the reactive derivatives of the compound (1e), common ester such as methylester, ethylester, tert-butyl ester and the like; acid halide such as acid chloride, acid bromide, and the like; acid azide; active ester with N-hydroxybenzotriazole, p-nitrophenol or N-hydroxysuccinimide or the like; symmetrical acid anhydride; acid anhydride mixture with alkyl carbonate, p-toluenesulfonic acid or the like can be exemplified.

[0027]

In case the compound (1e) is reacted as a free acid, or the active ester or acid halide is reacted without isolated, and the like, it is suitable to carry out the reaction using a condensing agent such as dicylcohexylcarbodiimide,

carbonyldiimidazole, diphenylphosphorylazide, diethylphosphorylcyanide, or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), and phosphorous oxychloride in pyridine solvent.

[0028]

The reaction is, although varies depending on the reactive derivatives or condensing agent, carried out in an inert organic solvent such as halogenated hydrocarbon including dichloromethane, dichloroethane, chloroform and the like; aromatic hydrocarbon including benzene, toluene, xylene and the like; ether including ether, tetrahydrofuran (THF) and the like; ester including ethyl acetate; N,N-dimethylformamide (DMF) or dimethylsulfoxide (DMSO), and the like, under cooling, cooling to room temperature, or room temperature to heating.

[0029]

In order to progress the reaction smoothly, it is advantageous in some cases to employ an excess amount of the compound (1e) or carry out the reaction in the presence of a base such as N-methylmorpholine, trimethylamine, triethylamine, N,N-dimethylaniline, pyridine, 4-(N,N-dimethylamino)pyridine, picoline, lutidine, and the like. And, a salt consisting of strong acid and weak base such as pyridine hydrochloride, pyridine p-toluenesulfonate, N,N-dimethylaniline hydrochloride and the like can be used. Pyridine can also be used as a solvent.

Particularly, it is advantageous to carry out the reaction in a solvent such as acetonitrile or DMF using a base such as pyridine or N,N-dimethylaniline, or using pyridine as a solvent.

[0030]

The starting material (1d) used in the reaction can be prepared by synthesizing a compound (1b) by halogenation of 5 position of a compound (1a) and then reacting the compound (1b) with a compound (1c). The compound (1b) can also be used in subsequent reaction without isolated.

[0031]

As a halogenation agent, those commonly used for halogen substitution reaction of hydrogen on aromatic ring can be used. Halogen atom such as chlorine, bromine and the like, dioxanedibromide, phenyltrimethylammonium tribromide, pyridine such as pyridinium hydrobromide perbromide, pyrrolidonehydrotribromide and the like, perbromide such as α-pyrrolidone, quaternary ammonium, dioxane and the like are appropriate. Imide type halogenation agent such as N-bromosuccinimide, N-chlorosuccinimide and the like, hydrogen halide such as hydrochloric acid, hydrobromic acid and the like, a metal agent such as copper (II) halide including copper bromide (II), copper chloride (II) and the like can also be used.

[0032]

In case a halogen or perbromide is used, the compound (1a) can be reacted in an inert organic solvent such as halogenated hydrocarbon; ether; alcohol including methanol (MeOH), ethanol (EtOH), 2-propanol, ethyleneglycol and the like; aromatic hydrocarbon; acetic acid; ester including ethyl acetate (EtOAc) and the like. If necessary, the reaction may be carried out in the presence of a small amount of a catalyst such as hydrogen halide. It is preferable to carry out the reaction at –30 ℃ to reflux temperature of the used solvent.

In case hydrogen halide is used as a halogenation agent, the compound (1a) can be reacted therewith in an acid solution or a base solution such as sodium hydroxide aqueous solution, and the reaction is preferably carried out at –30 ℃ to reflux temperature of the used solvent. And, in case a metal agent is used as a halogenation agent, the compound (1a) is generally dissolved in an inert organic solvent such as halogenated hydrocarbon, ether, alcohol, aromatic hydrocarbon, acetic acid, ester, and the like, or water, or a mixture thereof to react with the agent, and if necessary, it is advantageous to carry out the reaction in the presence of a small amount of a catalyst such as hydrogen halide, under room temperature to heating.

[0033]

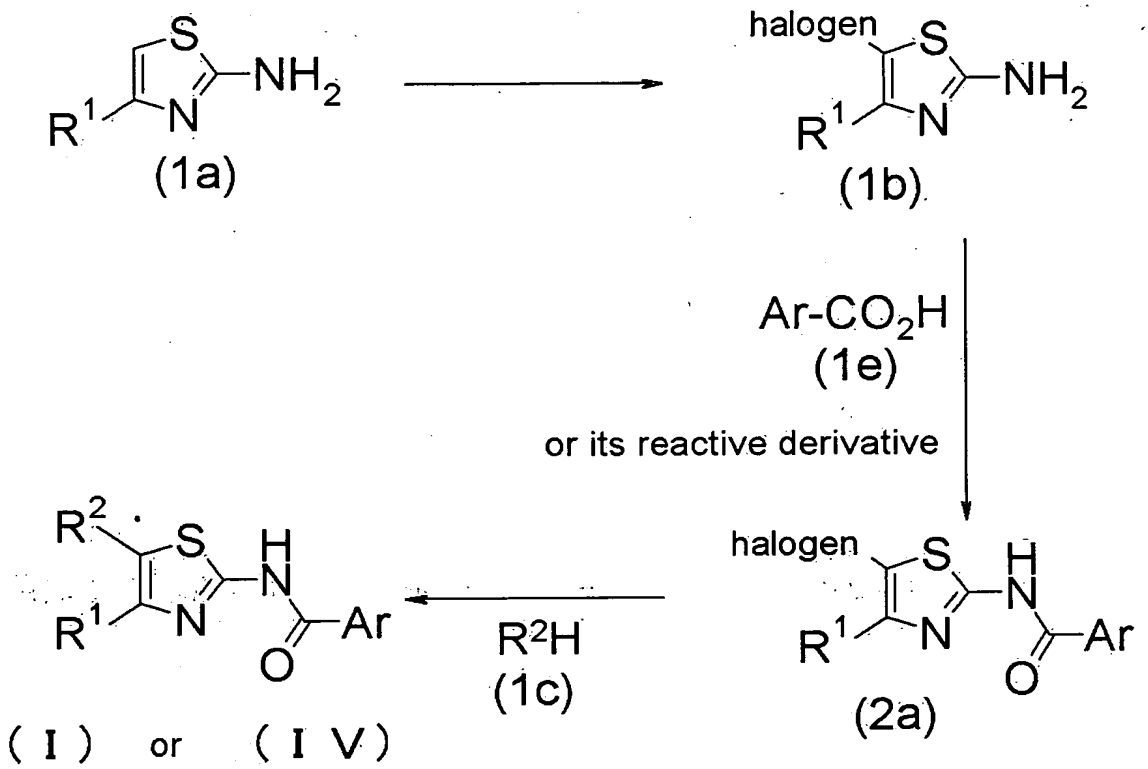
The thus obtained compound (1b) is reacted with the compound (1c) in a non-protonic polar solvent such as DMF, N-methyl-2-pyrrolidone, DMSO and the like, an inert organic solvent such as halogenated hydrocarbon, ether, aromatic hydrocarbon, or water, or a mixture thereof to prepare a compound (1d). The reaction is preferably carried out at room temperature to reflux temperature of the used solvent.

In order progress the reaction smoothly, it is advantageous in some cases to employ an excess amount of the compound (1e) or carry out the reaction in the presence of a base such as N-methylmorpholine, triethylamine, diethylisopropylamine, N,N-dimethylaniline, pyridine, 4-(N,N-dimethylamino)pyridine, picoline, lutidine and the like.

[0034]

(Second production method)

[Chemical Formula 11]



In this method, a compound (2a) is synthesized by the amidation of the compound (1b) synthesized by the first production method with a compound (1e) or its reactive derivative, and then reacted with a compound (1c), and if necessary a protection group is removed to prepare the compound (I) or (IV) of the present invention.

Any process can be carried out in accordance with the processes of the first production method.

[0035]

The thus produced compound of the present invention is isolated and purified as its free form or as a salt thereof. A salt of the compound (I) can be produced by subjecting it to a usual salt formation reaction. The

isolation and purification are carried out by usual chemical operations such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, various types of chromatography and the like.

Various types of isomers can be separated by usual method using the difference in physicochemical properties among isomers. For example, racemic mixture can be separated by a general racemic mixture resolution method, e.g., a method in which it is converted into diastereomer salts with an optically active acid such as tartaric acid and the like and then subjected to optical resolution. And, diastereomers can be separated by fraction crystallization or various types of chromatography or the like. And, optically active compounds can be prepared using appropriate optically active starting materials.

[0036]

[Effect of the invention]

The compound and its salt of the present invention have excellent effects of increasing platelets. Thus, the compound of the present invention is useful in the treatment and/or prevention of thrombocytopenia due to aplastic anemia, myelodysplastic syndrome, chemotherapy or radiotherapy for malignant tumor, idiopathic thrombocytopenic purpura, liver disease, HIV, and the like. In case thrombocytopenia is likely to be caused by chemotherapy or radiotherapy, it is possible to administrate the compound of the present invention prior to carrying out the therapy.

[0037]

Pharmaceutical efficacy of the compound of the present invention was confirmed by the following tests.

Effects of promoting the formation of megakaryocytic colonies

Human $CD34^+$ cells were cultured at 37 ℃ for 10-14 days, in the presence of tested materials, in a 2 well chamber slide, using MegaCult™-C (Stem Cell, Technologies Company). In accordance with the attached instructions, dehydration, fixing, and staining with anti-human glycoprotein IIb/IIIa antibody were carried out. A group of 3 or more of stained megakaryocytes was regarded as 1 colony, and the number of colonies per 1 well was measured by a microscope.

From these results, it has been confirmed that the compound of the present invention has excellent effects of promoting the formation of megakaryocytic colonies.

[0038]

A pharmaceutical composition of the present invention can be prepared by generally used methods using one or more kinds of the compound of the present invention of the general Formula (I) or (V) and pharmaceutical carriers, fillers and other additives generally used in the preparation of medicaments. It may be administrated either by oral administration through tablets, pills, capsules, granules, powders, solutions and the like, or by parenteral administration through injections such as intravenous injection, intramuscular injection and the like, or through suppositories, or pernasal, permucosal or percutaneous preparations and the like.

[0039]

The solid composition for use in the oral administration according to the present invention is used in the forms of tablets, powders, granules and the like. In such a solid composition, one or more active substances are

mixed with at least one kind of inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, metasilicate or magnesium aluminate. In the usual way, the composition may contain additives other than the inert diluent, which include a lubricant such as magnesium stearate, a disintegrating agent such as calcium cellulose glycolate, a stabilizing agent such as lactose and a solubilization assisting agent such as glutamic acid or aspartic acid. As occasion demands, tablets or pills may be coated with a sugar coat or a film of gastrosoluble or enterosoluble substance such as sucrose, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, or the like.

[0040]

The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contains a generally used inert diluent such as purified water or ethanol. In addition to the inert diluent, this composition may also contain auxiliary agents such as a moistening agent and a suspending agent, as well as a sweetener, a flavor, and aromatic and an antiseptic.

[0041]

The injections for parenteral administration include aseptic aqueous or non-aqueous solutions, suspensions and emulsions. Examples of the aqueous solutions and suspensions include distilled water for injection use and physiological saline. Examples of the non-aqueous solutions and suspensions include plant oil such as propylene glycol, polyethylene glycol, olive oil or the like, alcohol such as ethanol, polysorbate 80 (trade name) and

the like. Such a composition may further contain auxiliary agents such as an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizing agent (e.g., lactose) and a solubilization assisting agent (e.g., glutamic acid or aspartic acid. These compositions are sterilized for example by filtration through a bacteria retaining filter, blending of a germicide or irradiation. Alternatively, they may be used by firstly making into sterile solid compositions and dissolving them in sterile water or a sterile solvent for injection use prior to their use.

[0042]

In the case of oral administration, a daily dose is approximately 0.0001-50 mg/kg per body weight, preferably approximately 0.001-10 mg/kg, and more preferably approximately 0.01-1 mg/kg, and the daily dose is administered once a day or by dividing it into 2 to 4 doses per day. In the case of intravenous administration, a daily dose is approximately 0.0001-1 mg/kg per body weight, preferably approximately 0.0001-0.1 mg/kg, and the daily dose is administered once a day or by dividing it into plural doses per day. The dose is appropriately decided by taking symptoms, age and sex of the patient to be treated and the like into consideration.

[0043]

[Example]

The following describes the invention more illustratively with reference to examples, but the present invention is not limited to these examples. In this connection, novel materials are included in the starting materials to be used in the examples, and production methods of the starting materials from known materials are described as reference examples.

[0044]

Symbols in the Table have the following meanings.

Rf: Reference Example number, Ex: Example number

Salt: salt (HCl: hydrochloride, AcOH: acetate, TFA: trifluoroacetate, no description: free body)

Data: physical data (MS: FAB-MS(M+H)+; MN:FAB-MS(M-H)-; NMR: peaks δ (ppm) in ^{1}H-NMR using $(CH_3)_4Si$ as an internal standard, and DMSO-d_6 as measuring solvent unless otherwise indicated)

Syn: production method (The number indicates Reference Example or Example number used for synthesis)

R^1, R^2, Ar: substituent groups in the general Formula (Me: methyl, Et: ethyl, nPr: normal propyl, iPr: isopropyl, nBu: normal butyl, tBu: tertiary butyl, cBu: cyclobutyl, cPen : cyclopentyl, nHex: normal Hexyl, cHex: cyclohexyl, cHep: cycloheptyl, Ph: phenyl, Bn: benzyl, The: thienyl, Fur: furanyl, Py: pyridyl, Mor: morpholin-4-yl, Ac: acetyl, Ms: methanesufonyl, Imd: imidazol-1-yl, pipe: piperidinyl, pipa: piperazinyl, TBS: tertiary butyl dimethylsilyl, di: di (2 of the corresponding substituent groups substitute), The number before the substituent group indicates substitution position. Thus, for example, 5-Cl-3-The indicates 5-chlorothiophen-3-yl, 4-cHex-1-pipa 4-cyclohexylpiperazin-1-yl)

[0045]

Reference Example R1

To a solution of 6.0 g of 2-amino-4-(4-fluorophenyl)thiazole in 100 ml of THF, 1.60 ml of bromine was added dropwise, and the mixture was stirred at room temperature for 90 minutes. After evaporation of the solvent, 100

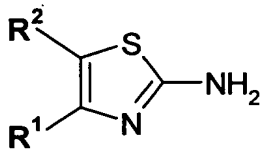
ml of DMF, 10.4 g of 1-cyclohexylpiperazine and 17.2 ml of triethylamine were added, and the mixture was stirred at 90 ℃ for 31 hours. The solvent was evaporated under reduced pressure, and the residue was mixed with saturated aqueous $NaHCO_3$ and extracted with chloroform. The organic layer was washed with brine, and dried over sodium sulfate. The residue obtained by the evaporation of the solvent under reduced pressure was purified by silica gel column chromatography (chloroform-MeOH = 100:1-100:3) to obtain 11.26 g of 2-amino-5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazole.

[0046]

Compounds of Examples R2-R11 as shown in Table 1 were synthesized in the same manner as described in Reference Example R1, employing each corresponding starting material.

[0047]

[Table 1]



Rf	Syn	R^1	R^2	Data
R1	R1	4-F-Ph	4-cHex-1-pipa	NMR(DMSO-d_6);1.05-1.27(5H,m),1.52-1.62(1H,m),1.68-1.82(4H,m),2.20-2.31(1H,m),2.58-2.66(4H,m),2.68-2.76(4H,m),6.81(2H,s),7.17(2H,t,J=9.0Hz),8.06-8.14(2H,m).
R2	R1	4-F-Ph	4-nPr-1-pipe	MS;320.
R3	R1	3-Cl-Ph	4-cHex-1-pipa	MS;377.
R4	R1	3-Br-Ph	4-cHex-1-pipa	MS;421,423.
R5	R1	3-CF_3-Ph	4-cHex-1-pipa	FAB-MS$(M)^+$;410.
R6	R1	3-Me-Ph	4-cHex-1-pipa	MS;357.
R7	R1	3,4-diF-Ph	4-cHex-1-pipa	MS;379.

R8	R1	3-Cl-4-F-Ph	4-cHex-1-pipa	MS;395.
R9	R1	4-F-Ph	1-pipe	MS;278.
R10	R1	4-F-Ph	4-nPr-pipa	MS;321.
R11	R1	4-F-Ph	4-nBu-pipa	MS;335.

[0048]

Reference Example R12

To a solution of 2.50 g of 3-chloro-4-hydroxybenzoic acid methyl ester in 25 ml of DMF, 2.78 g of potassium carbonate and 4.31 ml of 2-(tert-butyldimethylsilyloxy)ethylbromide were added, and the mixture was stirred at 50 ℃ for 15 hours. The solvent was evaporated, EtOAc was added to the residue, and the organic layer was washed with water and brine and dried over sodium sulfate. After the evaporation of the solvent, the obtained residue was purified by silica gel column chromatography (eluent: hexane-EtOAc = 10:1-5:1) to obtain 4.88 g of 4-[2-(tert-butyldimethylsilyloxy)ethoxy]-3-chlorobenzoic acid methyl ester.

[0049]

Reference Example R13

To a solution of 1.5 g of 3-chloro-4-hydroxybenzoic acid methyl ester in 20 ml of THF, 1.8 ml of 1-tert-butoxy-2-propanol, 3.16 g of triphenylphosphine and 1.9 ml of diethylazodicarboxylate were added, and the mixture was stirred at room temperature for 1 hour. After the evaporation of the solvent under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane-EtOAc = 100:1-5:1) to obtain 2.3 g of 4-(1-tert-butoxy-2-propoxy)-3-chlorobenzoic acid methyl ester.

[0050]

Reference Example R14

4.0 g of 6-quinolinecarboxylic acid was suspended in 30 ml of MeOH,

2.0 ml of conc. sulfate was added under ice cooling, and the mixture was stirred at 70 ℃ for 22 hours. The reaction solution was concentrated under reduced pressure, and the residue was mixed with water and neutralized with potassium carbonate. The thus precipitated solid was filtered and dried to obtain 4.28 g of 6-quinolinecarboxylic acid methyl ester. 0.5 g of the obtained ester body was dissolved in 5 ml of formamide, 0.15 ml of conc. sulfate, 0.05 g of ferrous sulfate hepta-hydrate, and 0.4 ml of 31% hydrogen peroxide were sequentially added thereto, and the mixture was stirred at 80 ℃ for 50 minutes. The reaction solution was mixed with water and alkalinized with potassium carbonate. 10% MeOH-chloroform was added, and insoluble matter was filtered using celite. The obtained filtrate was separated, the obtained organic layer was dried over anhydrous sodium sulfate and concentrated, and the obtained residue was washed with EtOH to obtain 0.15 g of 6-methoxycarbonyl-2-quinolinecarboxamide.

[0051]

Reference Example R15

To a solution of 1.96 g of 5-methylpyrazole-3-carboxylic acid ethyl ester in 40 ml of DMF, 2.64 g of potassium carbonate and 3.53 ml of 3-(tert-butyldimethylsilyloxy)propylbromide were added, and the mixture was stirred at 50 ℃ for 18 hours. The solvent was evaporated, EtOAc was added to the residue, and the organic layer was washed with water and brine and dried over sodium sulfate. After the evaporation of the solvent, the obtained residue was purified by a silica gel column chromatography (hexane-EtOAc = 15:1-5:1) to obtain 1.39 g of 1-[3-(tert-butyldimethylsilyloxy)propoxy]-5-methylpyrazole-3-carboxylic acid ethyl

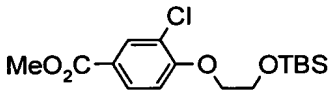
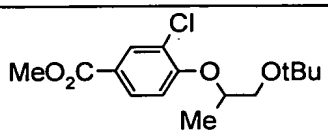
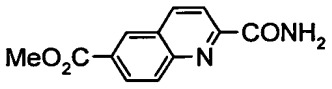
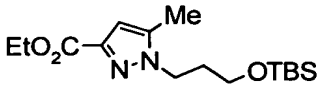
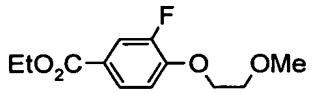
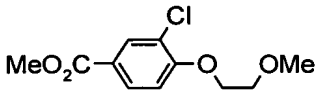
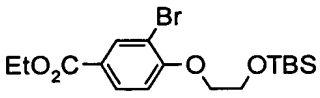
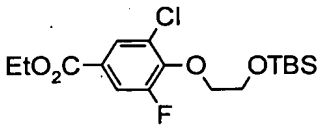
ester.

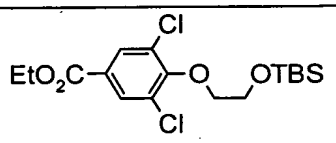
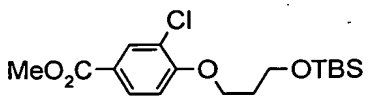
[0052]

Compounds of Examples R16-R21 as shown in Table 2 were synthesized in the same manner as described in Reference Example R12, employing each corresponding starting material.

[0053]

[Table 2]

Rf	Syn	structure	Data
R12	R12		MS;345.
R13	R13		MS;301.
R14	R14		MS;231.
R15	R15		MS;327.
R16	R12		MS;243.
R17	R12		MS;245.
R18	R12		MS;403,405.
R19	R12		NMR($CDCl_3$);0.05-0.13(6H,m),0.82-0.93(9H,m),1.40(3H,t,J=7.1Hz),3.97(2H,t,J=5.1Hz),4.28-4.34(2H,m),4.37(2H,q,J=7.1Hz),7.68(1H,dd,J=2.0,11.6Hz),7.87(1H,t,J=2.0Hz)

R20	R12		MS;393.
R21	R12		MS;359.

[0054]

Reference Example R22

To a solution of 2.16 g of the compound of Reference Example R12 in MeOH 20ml-THF 15 ml, 7.5 ml of 1M NaOH aq was added, and the mixture was stirred at room temperature for 3 days. The solvent was evaporated, and the residue was acidified with 5% potassium hydrogensulfate aq. and extracted with chloroform-2-propanol (3:1). The organic layer was washed with brine, and dried over sodium sulfate, and then the solvent was evaporated to obtain 1.17 g of 4-[2-(tert-butyldimethylsilyloxy)ethoxy]-3-chlorobenzoic acid.

[0055]

Reference Example R23

To 1.56 g of 3,4,5-trifluorobenzoylchloride, 6.32 ml of 2-methoyethanol and 6.53 g of cesium carbonate were added, and the mixture was stirred at 100 ℃ for 20 hours. The reaction solution was mixed with 50 ml of THF and filtered, and the filtrate was evaporated to obtain 4.36 g of colorless solid. The solid was dissolved in 15 ml of THF, 3.16 ml of 2-methoxyethanol and 1.35 g of potassium tert-butoxide were added thereto, and the mixture was stirred at room temperature for 4 days. The reaction solution was mixed with 5% potassium hydrogensulfate aq. and extracted with EtOAc, and then, the organic layer was washed with brine and dried over sodium sulfate. The

solution was evaporated to obtain 1.76 g of 3,5-difluoro-4-(2-methoxyethoxy)benzoic acid.

[0056]

Reference Example R24

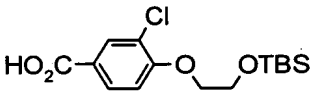
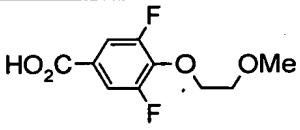
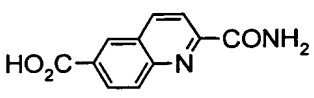
0.3 g of the compound of Reference Example R14 was dissolved in 10 ml of a mixed solvent of THF-MeOH (1:1), and 1.5 ml of 1M NaOH aq. was added at room temperature, and the mixture was stirred at the same temperature for 3 days. The reaction solution was concentrated under reduced pressure, mixed with water and neutralized with 1.5 ml of 1M HCl aq. The thus obtained solid was filtered and dried to obtain 0.29 g of 2-carbamoylquinoline-6-carboxylic acid.

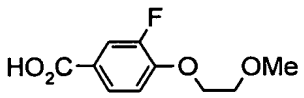
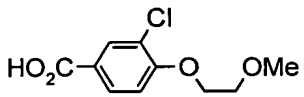
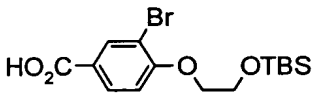
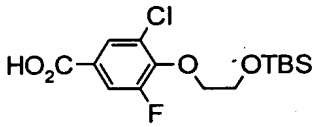
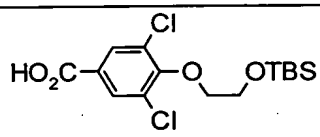
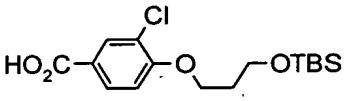
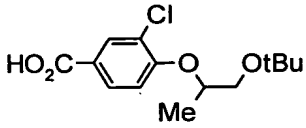
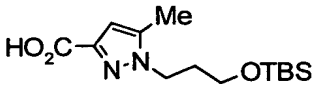
[0057]

Compounds of Reference Examples R25-R32 as shown in Table 3 were synthesized in the same manner as described in Reference Example R22, employing each corresponding starting material.

[0058]

[Table 3]

Rf	Syn	structure	Data
R22	R22		MN;329.
R23	R23		MN;231.
R24	R24		MN;215.

R25	R22		MN;213.
R26	R22		MN;229.
R27	R22		MN;373,375.
R28	R22		NMR($CDCl_3$);0.05-0.15(6H,m),0.85-0.92(9H,m),3.97(2H,t,J=5.2Hz),4.32-4.37(2H,m),7.73(1H,dd,J=2.0,11.2Hz),7.93(1H,t,J=2.0Hz).
R29	R22		MN;363.
R30	R22		MN;343.
R31	R22		MS;287.
R32	R22		MN;297.

[0059]

Reference Example R33

To a solution of 2.00 g of the compound of Reference Example R1 and 1.14 g of 4-formylbenzoic acid in 30 ml of DMF, 992 mg of N-hydroxybenzotriazole (HOBt) and 1.39 g of WSC·HCl were added, and the mixture was stirred at room temperature overnight. After the evaporation of the solvent under reduced pressure, the residue was mixed with saturated $NaHCO_3$ aq. and extracted with chloroform, and then the organic layer was

dried over $MgSO_4$. The residue obtained by the evaporation of the solvent was purified by silica gel column chromatography twice using chloroform: MeOH (100:1-30:1) and hexane: EtOAc (5:1-1:1) as an eluent to obtain 1.32 g of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-formylbenzamide.

FAB-MS$(M+H)^+$; 493

[0060]

Example 1

To a solution of 300 mg of the compound of Reference Example R1 in 5 ml of pyridine, 280 mg of 4-cyanobenzoylchloride was added, and the temperature was elevated to a room temperature, and then the mixture was stirred at the same temperature for 3 days and then at 50 ℃ for 1 day. The solvent was evaporated under reduced pressure, the residue was mixed with chloroform, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over sodium sulfate. After the evaporation of the solvent under reduced pressure, the obtained residue was recrystallized from EtOAc to obtain 230 mg of N-[5-(4-cyclohexypiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-cyanobenzamide. To a solution of 80 mg of the obtained compound in 5 ml of EtOAc, 0.4 ml of a solution of 0.4 M HCl-EtOAc was added, and the mixture was stirred overnight and filtered to obtain 57 mg of N-[5-(4-cyclohexylpiperzain-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-cyanobenzamide hydrochloride.

[0061]

Example 2

To a solution of 299 mg of the compound of Reference Example R2 in 7

ml of DMF, 211 mg of quinoline-6-carboxylic acid, 243 mg of WSC·HCl and 171 mg of HOBt were added, and the mixture was stirred at room temperature for 12 hours. The solvent was evaporated, and the residue was mixed with saturated aqueous sodium bicarbonate and extracted with chloroform, and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (chloroform) and dissolved in EtOAc, 0.5M HCl-EtOAc solution was added thereto, and the mixture was stirred, and then the produced precipitate was filtered to obtain 432 mg of N-[4-(4-fluorophenyl)-5-(4-propylpiperidin-1-yl)thiazol-2-yl]quinoline-6-carboxamide hydrochloride.

[0062]

Example 3

To a solution of 300 mg of the compound of Reference Example R1 in 5 ml of pyridine, 190 mg of quinoline-7-carboxylic acid was added, 0.10 ml of phosphorous oxychloride was added at -25 ℃, the temperature was elevated to room temperature and the mixture was stirred for 4 days. The solvent was evaporated, and the residue was mixed with sodium bicarbonate and extracted with chloroform, and the organic layer was washed with brine and dried over sodium sulfate. After evaporation of the solvent, the obtained residue was purified by silica gel column chromatography (chloroform-MeOH = 100:0-99:1) and suspended in 5 ml of EtOAc, 0,35 ml of 4M HCl-EtOAc solution was added thereto, and the mixture was stirred, and then the produced precipitate was filtered to obtain 397 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]quinoline-7-carboxamide hydrochloride.

[0063]

Example 4

To a suspension of 180 mg of the compound of Example 64 in 5 ml of DMF, 100 mg of 1,1'-carbonyldimidazole was added, and the mixture was stirred at room temperature for 4 days. Then, 1 ml of 28% ammonia aq. was added, and the mixture was stirred at room temperature for 1.5 hours. The reaction solution was mixed with water and extracted with chloroform. The organic layer was dried over MgSO4, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethanol, and suspended in EtOH. Then, 0.35 ml of 1M HCl-EtOAc solution was added thereto, the mixture was stirred overnight, and the thus produced precipitate was collected by filtration to obtain 151 mg of N-[4-(4-fluorophenyl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]-4-carbamoylmethylbenzamide hydrochloride.

[0064]

Example 5

To 138 mg of the compound of Example 42, 3 ml of water and 3 ml of conc. HCl were added, and the mixture was stirred at 80 ℃ for 17 hours. The reaction solution was cooled to a room temperature, and the thus produced precipitate was collected by filtration and washed with water. 1M aqueous NaOH, MeOH and diethylether were added thereto, and insoluble matter was removed by filtration. The obtained filtrate was extracted with diethylether, and conc. HCl was added to the aqueous layer, and the thus produced precipitate was collected by filtration and dried under reduced pressure to obtain 101 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-

fluorophenyl)thiazol-2-yl]-4-(3,4-dioxo-2-hydroxycyclobut-1-en-1-yl)amino]benzamide hydrochloride.

[0065]

Example 6

To 430 mg of the compound of Example 60, 15 ml of water and 15 ml of conc. HCl were added, and the mixture was stirred at 80 ℃ for 3.5 hours. The reaction solution was cooled to 0 ℃, 50 ml of water was added thereto, and the thus produced precipitated was collected by filtration and dried under reduced pressure to obtain 101 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-2,3-dihydroxyquinoxaline-6-carboxamide hydrochloride.

[0066]

Example 7

To a suspension of 0.30 g of the compound of Example 23 in 5 ml of MeOH, 1 ml of conc. hydrochloric acid was added under ice cooling, and the mixture was stirred at 50 ℃ overnight. The reaction solution was cooled to room temperature, and the precipitated solid was filtered and dried to obtain 268 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-(4-hydroxyphenyl)benzamide hydrochloride.

[0067]

Example 8

To a solution of 1.72 g of the compound of Reference Example R12 in a mixed solvent of MeOH 17ml-THF 10ml, 6 ml of 1M NaOH aq. was added, and the mixture was stirred at room temperature for 3 days. To the reaction solution, 5.5 ml of 1M HCl aq. was added, and solvent was

evaporated under reduced pressure to obtain a crude product of 4-[2-(tert-butyldimethylsilyloxy)ethoxy]-3-chlorobenzoic acid. To the obtained crude product, 720 mg of the compound of Reference Example 1, 20 ml of DMF, 959 mg of WSC·HCl, 676 mg of HOBt and 611 mg of 4-(dimethylamino)pyridine were added, and the mixture was stirred at 50 ℃ for 22 hours and then at 90 ℃ for 20 hours. The solvent was evaporated, the residue was mixed with saturated aqueous $NaHCO_3$ and extracted with EtOAc, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over sodium sulfate. After the evaporation of the solvent, the residue was purified by silica gel column chromatography using chloroform-MeOH (100:1-10:1) as an eluent and a silica gel column chromatography using hexane:EtOAc (2:1-1:1) as an eluent to obtain 38 mg of 3-chloro-4-{2-[3-chloro-4-(2-hydroxyethoxy)benzoyloxy]ethoxy}-N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]benzamide. To the obtained compound, 0.5 ml of MeOH, 1 ml of THF, and 225 μl of 1M NaOH aq. were added, and the mixture was stirred at room temperature for 5 days. The reaction solution was mixed with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and dried over sodium sulfate. After the evaporation of the solvent, the residue was purified by a silica gel chromatography (chloroform-MeOH = 100:0~100:2) and dissolved in 5 ml of EtOAc, 1.0 ml of 0.1 M HCl-EtOAc solution was added, the mixture was stirred for a while, and the produced precipitate was collected by filtration to obtain 18 mg of 3-chloro-N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-(2-hydroxyethoxy)benzamide hydrochloride.

[0068]

Example 9

To a suspension of 0.09 g of the suspension of Example 36 in 2 ml of EtOAc, 1 ml of 4M hydrochloric acid-EtOAc solution were added under ice cooling, and the mixture was stirred at room temperature for 1 day. The precipitate solid was filtered and dried to obtain 81 mg of 4-(aminomethyl)-N-[5-(4-cyclohezylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]benzamide hydrochloride.

[0069]

Example 10

To a solution of 100 mg of the compound of Reference Example R33 in 5 ml of MeOH, 24 mg of sodium borohydride was added at 0 ℃, and the mixture was stirred at room temperature for 1 hour. 2 ml of DMF was added thereto, and the mixture was stirred for 1hour, and 36 mg of the sodium borohydride was added and the mixture was stirred for 1 hour again. The reaction solution was poured into 1M aqueous HCl, alkalinized with saturated aqueous $NaHCO_3$, and extracted with chloroform, and the organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (chloroform-MeOH = 100:1-20:1) and dissolved in EtOAc, and then 0.5M HCl-EtOAc solution was added thereto and the thus produced precipitate was collected by filtration to obtain 73 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-hydroxymethylbenzamide hydrochloride.

[0070]

Example 11

200 mg of the compound of Example 66 and 0.1 ml of 35% formaldehyde solution were dissolved in 5 ml of methylene chloride-0.5 ml of acetic acid, 200 mg of sodium triacetoxyborohydride was added thereto at 0 ℃, and the mixture was stirred at the same temperature overnight. And, 0.1 ml of 35% formaldehyde and 100 mg of sodium triacetoxyborohydride were added thereto, and the mixture was stirred at the same temperature for 2 hours. The reaction solution was alkalinized with aqueous potassium carbonate, and then extracted with chloroform, and the organic layer was dried over magnesium sulfate, and then the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (chloroform-MeOH=98:4-96:4) and dissolved in 5 ml of EtOH. 0.3 ml of 4M HCl-EtOAc solution was added thereto, and the mixture was stirred overnight. The thus produced precipitate was collected by filtration to obtain 144 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-(4-methylpiperazin-1-yl)benzamide hydrochloride.

[0071]

Example 12

To a suspension of 279 mg of the compound of Example 19 in 10 ml of toluene, 1.81 g of tributyltin azide was added, and the mixture was heated under reflux for 14 hours. And, diethylether, 1M aqueous NaOH, EtOAc, and conc. HCl were added thereto. The thus produced precipitate was collected by filtration and dried under reduced pressure, and then dissolved in 1M aqueous NaOH and MeOH, and washed with diethylether. To the aqueous layer, conc. HCl was added under 0 ℃ cooling, and the thus

produced precipitate was collected by filtration to obtain 138 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-(1H-tetrazol-5-ylmethyl)benzamide.

[0072]

Example 13

0.15 g of the compound of Example 9 was dissolved in 10 ml of THF, 0.1 ml of triethylamine and a solution of 40 mg of methyl chloroformate in 2 ml of THF were sequentially added thereto, and the mixture was stirred at room temperature overnight. The reaction solution was concentrated, mixed with water, and extracted with EtOAc. The obtained organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure, and the thus obtained residue was recrystallized from EtOAc to obtain 0.12 g of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-(methoxycarbonylaminomethyl)benzamide. The obtained compound was suspended in 5 ml of EtOAc, 0.6 ml of 0.4M HCl-EtOAc solution was added thereto under ice cooling, and the mixture was stirred overnight. The thus precipitated sold was filtered and dried to obtain 115 mg of N-[5-(4-cylcohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-(methoxycarbonylaminomethyl)benzamide hydrochloride.

[0073]

Example 14

0.15 g of the compound of Example 9 was suspended in 5 ml of THF, 0.2 ml of triethylamine and a solution of 35 mg of methanesulfonyl chloride in 2 ml of THF were sequentially added thereto under ice cooling, and the

mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated, mixed with water, and extracted with EtOAc. The obtained organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure, and the thus obtained residue was recrystallized from EtOAc-hexane mixed solvent to obtain 0.12 g of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-(methanesulfonylaminomethyl)benzamide. The obtained compound was suspended in 5 ml of EtOAc, 0.2 ml of 1M HCl-EtOAc solution was added under ice cooling, and the mixture was stirred overnight. The thus precipitated solid was filtered and dried to obtain 111 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-(methanesulfonylaminomethyl)benzamide hydrochloride.

[0074]

Example 15

To a solution of 57 mg of the compound of Example 67 in 2 ml of pyridine, 18 μl of methyl chlorooxoacetate was added, and the mixture was stirred from 0 ℃ to room temperature for 2 hours. After the solvent was evaporated under reduced pressure, the residue was mixed with saturated aqueous $NaHCO_3$ and extracted with chloroform, and the organic layer was dried over $MgSO_4$. Then, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (chloroform-MeOH=100:1). And, diisopropyl ether was added thereto, and the thus produced precipitate was collected by filtration to obtain 19 mg of methyl N-(4-{[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]carbamoyl}phenyl)oxalate.

[0075]

Example 16

To a suspension of 71 mg of the compound of Example 67 in 5 ml of DMF, 71 mg of 3-methoxypropionic acid, 120 mg of HOBt and 180 mg of WSC·HCl were added, and the mixture was stirred from room temperature to 50 ℃ for 29 consecutive days. After the solvent was evaporated under reduced pressure, the residue was mixed with saturated aqueous $NaHCO_3$ and extracted with chloroform, and the organic layer was dried over $MgSO_4$. Then, the residue obtained by the evaporation of the solvent was purified by silica gel column chromatography (chloroform-MeOH = 100:1-50:1). And, the reaction solution was mixed with MeOH and 1M aqueous HCl, and purified by ODS column chromatography (0.001M HCl aq-MeOH = 2:1-1:1), and then mixed with saturated aqueous $NaHCO_3$ and extracted with chloroform. After the organic layer was dried over $MgSO_4$, the solvent was evaporated, diisopropyl ether was added thereto, and the thus produced precipitate was collected by filtration to obtain 20 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]-4-[(3-methoxypropanoyl)amino]benzamide.

[0076]

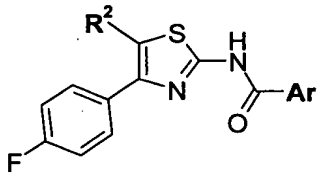
Example 17

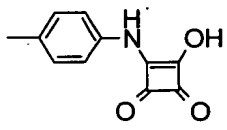
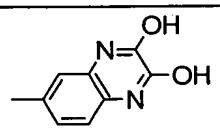
To a solution of 488 mg of the compound of Example 41 in 8 ml of MeOH, 1.7 ml of 1M aqueous NaOH were added, and the mixture was stirred at room temperature for 9 hours. To the reaction solution, 1.7 ml of 1M aqueous HCl was added, and the produced precipitate was collected by filtration, washed with water and MeOH, dried under reduced pressure, and

suspended in 10 ml of EtOAc. And, 2.5 ml of 0.1M HCl-EtOAc solution was added thereto, and the mixture was stirred for 3 hours, and then the produced precipitate was collected by filtration to obtain 109 mg of (2-chloro-4-{[5-(4-cyclohezylpiperazin-1-yl)-4-(4-fluorophenyl)thiazol-2-yl]carbamoyl}phenoxy)acetic acid hydrochloride.

[0077]

[Table 4]



Ex (Salt)	R^2	Ar	Data
1 (HCl)	4-cHex-1-pipa	4-NC-Ph	MS;490.
2 (HCl)	4-nPr-1-pipe	quinolin-6-yl	NMR;0.90(3H,t,J=7.1Hz),1.23-1.45(7H,m),1.77(2H,d,J=10.8Hz),2.66(2H,t,J=10.3Hz),3.15(2H,d,J=11.7Hz),7.29(2H,t,J=9.1Hz),8.00(1H,dd,J=4.7Hz,8.6Hz),8.17-8.20(2H,m),8.40(1H,d,J=8.8Hz),8.56(1H,dd,J=2.0Hz,8.8Hz),9.01(1H,d,J=1.5Hz),9.03(1H,s),9.29(1H,dd,J=1.5Hz,4.9Hz),12.50-13.00(1H,br). MS;475.
3 (HCl)	4-cHex-1-pipa	quinolin-7-yl	MS;516.
4 (HCl)	4-cHex-1-pipa	4-H_2NOCCH_2-Ph	MS;522.
5 (HCl)	4-cHex-1-pipa		MS;576.
6 (HCl)	4-cHex-1-pipa		MS;549.
7 (HCl)	4-cHex-1-pipa	4-(4-HO-PhO)-Ph	MS;573.
8 (HCl)	4-cHex-1-pipa	3-Cl-4-$HOCH_2CH_2O$-Ph	MS;559.

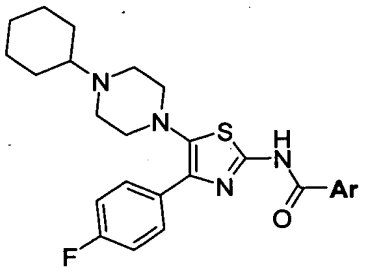
9 (HCl)	4-cHex-1-pipa	4-H_2NCH_2-Ph	MS;494.
10 (HCl)	4-cHex-1-pipa	4-$HOCH_2$-Ph	MS;495.
11 (HCl)	4-cHex-1-pipa	4-(4-Me-1-pipa)-Ph	MS;563.
12	4-cHex-1-pipa	4-(1H-tetrazol-5-yl)CH_2-Ph	MS;547.
13 (HCl)	4-cHex-1-pipa	4-MeO_2CHNCH_2-Ph	MS;552.
14 (HCl)	4-cHex-1-pipa	4-$MsHNCH_2$-Ph	MS;572.
15	4-cHex-1-pipa	4-MeO_2COCHN-Ph	MS;566.
16	4-cHex-1-pipa	4-$MeOCH_2CH_2OCHN$-Ph	MS;566.
17 (HCl)	4-cHex-1-pipa	3-Cl-4-HO_2CCH_2O-Ph	MS;573.

[0078]

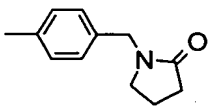
Compounds of Examples 18-70 as shown in Tables 5-7 were synthesized in the same manner as described in the Example, employing each corresponding starting material.

[0079]

[Table 5]

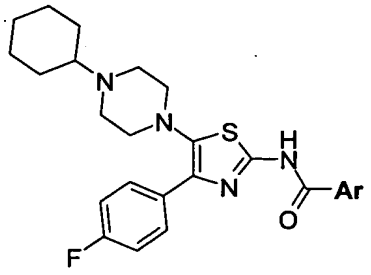


Ex (Salt)	Syn	Ar	Data
18 (HCl)	1	3-NC-Ph	MS;490.
19 (HCl)	2	4-$NCCH_2$-Ph	MS;504.
20 (HCl)	3	4-$NCCH_2CH_2$-Ph	MS;518.
21 (HCl)	3	4-(NCCH=CH)-Ph	MS;516.
22 (HCl)	2	4-PhO-Ph	MS;557.

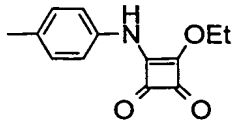
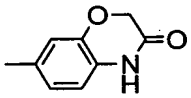
23	3	4-(4-$MeOCH_2O$-PhO)-Ph	MS;617.
24 (HCl)	1	3-F-4-F_3C-Ph	MS;551.
25 (HCl)	2	4-Me_2NCH_2-3-F-Ph	MS;540.
26 (HCl)	2	4-$Me_2NCH_2CH_2O$-3-F-Ph	MS;570.
27 (HCl)	2	3-Cl-4-$MeOCH_2CH_2O$-Ph	MS;573.
28 (HCl)	2	4-HO-3-MorCH_2-Ph	MS;580.
29	2	4-HO_3S-Ph	MS;545.
30	3	4-(4-$tBuO_2C$-1-pipa)-Ph	MS;649.
31 (HCl)	3	4-(4-Ac-1-pipa)-Ph	MS;591.
32 (HCl)	3	4-Mor-Ph	MS;550.
33 (HCl)	2	4-$AcOCH_2$-Ph	MS;537.
34 (HCl)	2	4-$AcHNCH_2$-Ph	MS;536.
35 (HCl)	2		MS;562.
36	2	4-$tBuO_2CHNCH_2$-Ph	MS;594.
37 (HCl)	2	4-$H_2NOCHNCH_2$-Ph	MS;537.
38 (HCl)	2	4-MsHN-Ph	MS;558.
39 (HCl)	2	4-$H_2NO_2SHNCH_2$-Ph	MS;573.
40	2	4-$tBuO_2CHN$-Ph	MS;580.

[0080]

[Table 6]

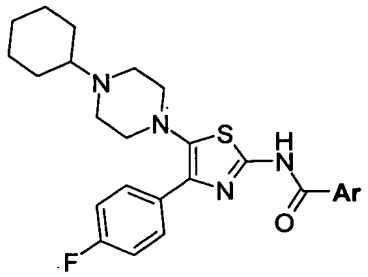


Ex (Salt)	Syn	Ar	Data
41 (HCl)	2	3-Cl-4-MeO_2CCH_2O-Ph	MS;587.

42 (HCl)	2		MS;604.
43 (HCl)	3	4-MeO_2CCH_2-Ph	MS;537.
44 (HCl)	3	3-MeO_2CCH_2-Ph	MS;537.
45 (HCl)	1	naphthalen-2-yl	MS;515.
46 (HCl)	2	quinolin-2-yl	MS;516.
47 (HCl)	2	isoquinolin-3-yl	MS;516.
48 (HCl)	2	quinolin-3-yl	MS;516.
49 (HCl)	2	quinolin-6-yl	MS;516.
50 (HCl)	3	isoquinolin-7-yl	MS;516.
51 (HCl)	3	quinolin-4-yl	MS;516.
52 (HCl)	2	2-HO-quinolin-6-yl	MS;532.
53 (HCl)	3	2-MeO-quinolin-6-yl	MS;546.
54 (HCl)	2	benzimidazol-5-yl	MS;505.
55	2	indol-5-yl	FAB-MS$(M)^+$;503.
56 (HCl)	3		MS;536.
57 (HCl)	2	6-HO-naphthalen-2-yl	MS;531.
58 (HCl)	2	imidazo[1,2-a]pyridin-6-yl	MS;505.
59 (HCl)	2	2-Me-isoindolin-5-yl	MS;520.
60	3	2,3-diBnO-quinoxalin-6-yl	MS;729.
61 (HCl)	1	benzodioxolan-5-yl	MS;509.

[0081]

[Table 7]



Ex (Salt)	Syn	Ar	Data
62 (HCl)	17	4-HO_2CCH_2HN-Ph	MS;538.
63	17	4-HO_2COCHN-Ph	MS;552.
64 (HCl)	17	4-HO_2CCH_2-Ph	MS;523.
65 (HCl)	17	3-HO_2CCH_2-Ph	MS;523.
66 (HCl)	9	4-(1-pipa)-Ph	MS;549.
67 (HCl)	9	4-H_2N-Ph	MS;480.
68 (HCl)	11	4-EtO_2CCH_2HN-Ph	MS;566.
69 (HCl)	4	3-H_2NOCCH_2-Ph	MS;522.
70 (HCl)	15	4-$MeOCH_2OCHN$-Ph	MS;552.

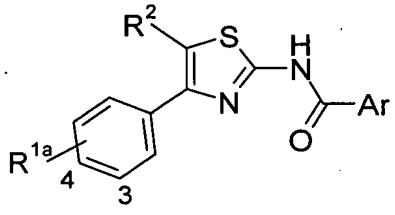
[0082]

The structures of the compounds of the invention are shown in Tables 8-22. These compounds can be easily synthesized by the above described production methods, methods described in Examples or modified methods thereof.

The No in the Tables indicates compound number.

[0083]

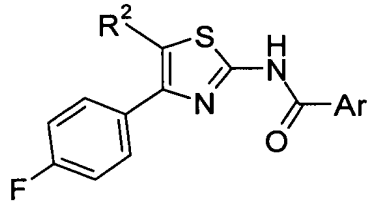
[Table 8]



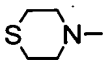
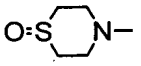
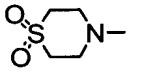
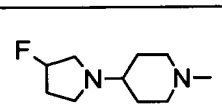
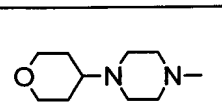
No	R^{1a}	R^2	Ar
A1	3-CF_3	4-cHex-1-pipa	quinolin-6-yl
A2			3-Cl-4-$HOCH_2CH_2O$-Ph
A3			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A4	3-Br		quinolin-6-yl
A5			3-Cl-4-$HOCH_2CH_2O$-Ph
A6			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A7	3-Cl		quinolin-6-yl
A8			3-Cl-4-$HOCH_2CH_2O$-Ph
A9			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A10	3-F		quinolin-6-yl
A11			3-Cl-4-$HOCH_2CH_2O$-Ph
A12			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A13	3-Me		quinolin-6-yl
A14			3-Cl-4-$MeOCH_2CH_2O$-Ph
A15			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A16	3-tBu		quinolin-6-yl
A17			3-Cl-4-$HOCH_2CH_2O$-Ph
A18			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A19	4-F		5-Cl-6-$HO(CH_2)_3NH$-3-Py
A20	3,4-diF		quinolin-6-yl
A21			3-Cl-4-$MeOCH_2CH_2O$-Ph
A22			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A23	3-Cl-4-F		quinolin-6-yl
A24			3-Cl-4-$HOCH_2CH_2O$-Ph
A25			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A26	4-F	4-nPr-1-pipa	quinolin-6-yl
A27			3-Cl-4-$HOCH_2CH_2O$-Ph
A28			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A29	3-Cl		quinolin-6-yl
A30			3-Cl-4-$HOCH_2CH_2O$-Ph
A31			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A32	3-CF_3		quinolin-6-yl
A33			3-Cl-4-$HOCH_2CH_2O$-Ph
A34			5-Cl-6-$HO(CH_2)_3NH$-3-Py
A35	4-F	Mor	quinolin-6-yl
A36			3-Cl-4-$HOCH_2CH_2O$-Ph
A37			5-Cl-6-$HO(CH_2)_3NH$-3-Py

[0084]

[Table 9]

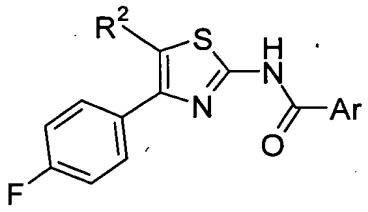


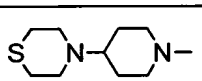
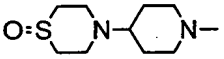
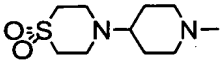
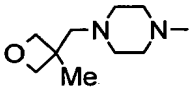
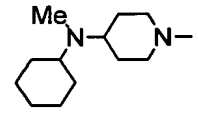
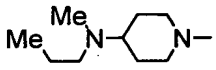
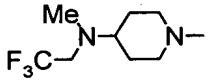
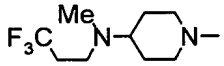
No	R^2	Ar
B1		qinolin-6-yl

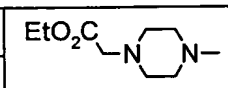
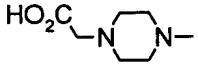
B2		3-Cl-4-$HOCH_2CH_2O$-Ph
B3		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B4		quinolin-6-yl
B5		3-Cl-4-$HOCH_2CH_2O$-Ph
B6		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B7		quinolin-6-yl
B8		3-Cl-4-$HOCH_2CH_2O$-Ph
B9		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B10	4-nBu-1-pipa	quinolin-6-yl
B11		3-Cl-4-$HOCH_2CH_2O$-Ph
B12		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B13	4-(3-Pentyl)-1-pipa	quinolin-6-yl
B14		3-Cl-4-$HOCH_2CH_2O$-Ph
B15		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B16	4-Pr-3,5-diMe-1-pipa	quinolin-6-yl
B17		3-Cl-4-$HOCH_2CH_2O$-Ph
B18		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B19	4-cPent-1-pipa	quinolin-6-yl
B20		3-Cl-4-$HOCH_2CH_2O$-Ph
B21		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B22	4-cHept-1-pipa	quinolin-6-yl
B23		3-Cl-4-$HOCH_2CH_2O$-Ph
B24		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B25	4-nPr-1-pipe	3-Cl-4-$HOCH_2CH_2O$-Ph
B26		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B27	4-(1-pipe)-1-pipe	quinolin-6-yl
B28		3-Cl-4-$HOCH_2CH_2O$-Ph
B29		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B30	4-(4-F-1-pipe)-1-pipe	quinolin-6-yl
B31		3-Cl-4-$HOCH_2CH_2O$-Ph
B32		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B33		quinolin-6-yl
B34		3-Cl-4-$HOCH_2CH_2O$-Ph
B35		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B36		quinolin-6-yl
B37		3-Cl-4-$HOCH_2CH_2O$-Ph
B38		5-Cl-6-$HO(CH_2)_3NH$-3-Py

[0085]

[Table 10]

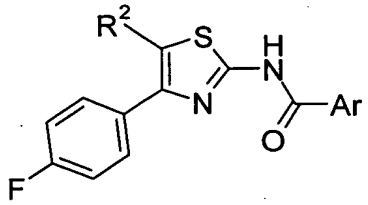


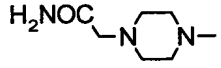
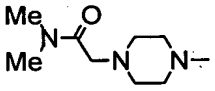
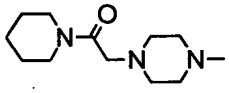
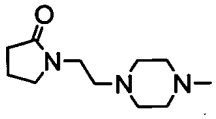
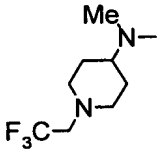
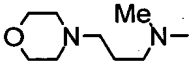
No	R^2	Ar
B39		3-Cl-4-$HOCH_2CH_2O$-Ph
B40		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B41		quinolin-6-yl
B42		3-Cl-4-$HOCH_2CH_2O$-Ph
B43		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B44		quinolin-6-yl
B45		3-Cl-4-$HOCH_2CH_2O$-Ph
B46		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B47		quinolin-6-yl
B48		3-Cl-4-$HOCH_2CH_2O$-Ph
B49		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B50	4-(4-F-cHex)-1-pipa	quinolin-6-yl
B51		3-Cl-4-$HOCH_2CH_2O$-Ph
B52		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B53	4-(4-MeO-cHex)-1-pipa	quinolin-6-yl
B54		3-Cl-4-$HOCH_2CH_2O$-Ph
B55		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B56	4-(4-CF_3-cHex)-1-pipa	quinolin-6-yl
B57		3-Cl-4-$HOCH_2CH_2O$-Ph
B58		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B59		quinolin-6-yl
B60		3-Cl-4-$HOCH_2CH_2O$-Ph
B61		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B62		quinolin-6-yl
B63		3-Cl-4-$HOCH_2CH_2O$-Ph
B64		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B65		quinolin-6-yl
B66		3-Cl-4-$HOCH_2CH_2O$-Ph
B67		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B68		quinolin-6-yl
B69		3-Cl-4-$HOCH_2CH_2O$-Ph
B70		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B71		quinolin-6-yl

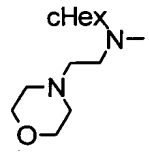
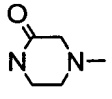
B72		3-Cl-4-$HOCH_2CH_2O$-Ph
B73		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B74		quinolin-6-yl
B75		3-Cl-4-$HOCH_2CH_2O$-Ph
B76		5-Cl-6-$HO(CH_2)_3NH$-3-Py

[0086]

[Table 11]

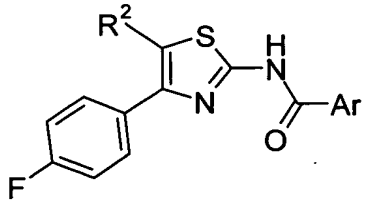


No	R^2	Ar
B77		quinolin-6-yl
B78		3-Cl-4-$HOCH_2CH_2O$-Ph
B79		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B80		quinolin-6-yl
B81		3-Cl-4-$HOCH_2CH_2O$-Ph
B82		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B83		quinolin-6-yl
B84		3-Cl-4-$HOCH_2CH_2O$-Ph
B85		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B86		quinolin-6-yl
B87		3-Cl-4-$HOCH_2CH_2O$-Ph
B88		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B89		quinolin-6-yl
B90		3-Cl-4-$HOCH_2CH_2O$-Ph
B91		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B92		quinolin-6-yl
B93		3-Cl-4-$HOCH_2CH_2O$-Ph
B94		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B95		quinolin-6-yl

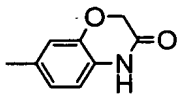
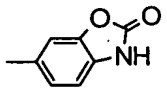
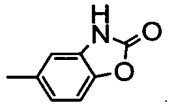
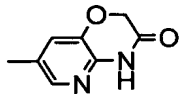
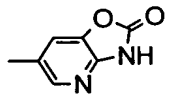
B96		3-Cl-4-$HOCH_2CH_2O$-Ph
B97		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B98		quinolin-6-yl
B99		3-Cl-4-$HOCH_2CH_2O$-Ph
B100		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B101	1-pipe	quinolin-6-yl
B102		3-Cl-4-$HOCH_2CH_2O$-Ph
B103		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B104	4-F-1-pipe	quinolin-6-yl
B105		3-Cl-4-$HOCH_2CH_2O$-Ph
B106		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B107	3-(Me_2NCH_2)-1-pipe	quinolin-6-yl
B108		3-Cl-4-$HOCH_2CH_2O$-Ph
B109		5-Cl-6-$HO(CH_2)_3NH$-3-Py
B110	2-(Me_2NCH_2)-1-pipe	quinolin-6-yl
B111		3-Cl-4-$HOCH_2CH_2O$-Ph
B112		5-Cl-6-$HO(CH_2)_3NH$-3-Py

[0087]

[Table 12]

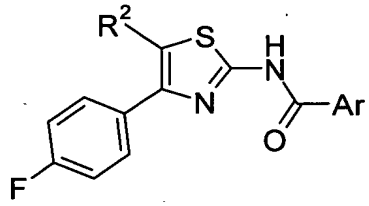


No	R^2	Ar
C1	4-nPr-1-pipa	2-hydroxyquinolin-6-yl
C2	4-nPr-1-pipe	
C3	4-cHex-1-pipa	3-hydroxyquinolin-7-yl
C4	4-nPr-1-pipa	
C5	4-nPr-1-pipe	
C6	4-cHex-1-pipa	7-hydroxyqionolin-3-yl
C7	4-nPr-1-pipa	
C8	4-nPr-1-pipe	
C9	4-cHex-1-pipa	2-methoxycarbonylquinolin-6-yl
C10	4-nPr-1-pipa	
C11	4-nPr-1-pipe	
C12	4-cHex-1-pipa	2-carboxyquinolin-6-yl
C13	4-nPr-1-pipa	
C14	4-nPr-1-pipe	
C15	4-cHex-1-pipa	2-carbamoylquinolin-6-yl
C16	4-nPr-1-pipa	
C17	4-nPr-1-pipe	
C18	4-cHex-1-pipa	2-hydroxymethylquinolin-6-yl

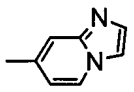
C19	4-nPr-1-pipa	
C20	4-nPr-1-pipe	
C21	4-cHex-1-pipa	2-methoxymethylquinolin-6-yl
C22	4-nPr-1-pipa	
C23	4-nPr-1-pipe	
C24	4-nPr-1-pipa	
C25	4-nPr-1-pipe	
C26	4-nPr-1-pipa	
C27	4-nPr-1-pipe	
C28	4-cHex-1-pipa	
C29	4-nPr-1-pipa	
C30	4-nPr-1-pipe	
C31	4-cHex-1-pipa	
C32	4-nPr-1-pipa	
C33	4-nPr-1-pipe	
C34	4-cHex-1-pipa	
C35	4-nPr-1-pipa	
C36	4-nPr-1-pipe	
C37	4-cHex-1-pipa	isoquinolin-6-yl
C38	4-nPr-1-pipa	
C39	4-nPr-1-pipe	

[0088]

[Table 13]

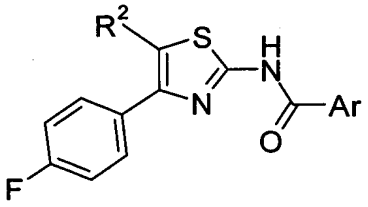


No	R^2	Ar
C40	4-nPr-1-pipa	isoquinolin-7-yl
C41	4-nPr-1-pipe	
C42	4-nPr-1-pipa	quinolin-7-yl
C43	4-nPr-1-pipe	
C44	4-nPr-1-pipa	quinolin-3-yl
C45	4-nPr-1-pipe	
C46	4-cHex-1-pipa	2-hydroxyquinoxalin-6-yl
C47	4-nPr-1-pipa	
C48	4-nPr-1-pipe	
C49	4-cHex-1-pipa	benzoxazol-6-yl

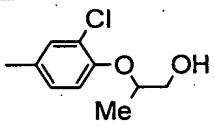
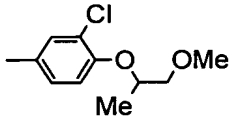
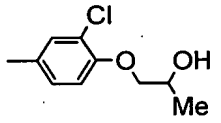
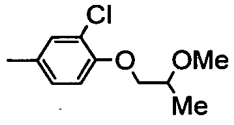
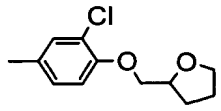
C50	4-nPr-1-pipa	
C51	4-nPr-1-pipe	
C52	4-cHex-1-pipa	1-methyl-1,2,3,4-tetrahydroquinolin-6-yl
C53	4-nPr-1-pipa	
C54	4-nPr-1-pipe	
C55	4-cHex-1-pipa	1-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl
C56	4-nPr-1-pipa	
C57	4-nPr-1-pipe	
C58	4-cHex-1-pipa	
C59	4-nPr-1-pipa	
C60	4-nPr-1-pipe	
C61	4-cHex-1-pipa	1-methyl-3,4-dyhydro-2H-1,4-benzoxazin-7-yl
C62	4-nPr-1-pipa	
C63	4-nPr-1-pipe	
C64	4-cHex-1-pipa	3-F-4-HO$(CH_2)_2$O-Ph
C65	4-nPr-1-pipa	
C66	4-nPr-1-pipe	
C67	4-cHex-1-pipa	3-Br-4-HO$(CH_2)_2$O-Ph
C68	4-nPr-1-pipa	
C69	4-nPr-1-pipe	
C70	4-cHex-1-pipa	3-Me-4-HO$(CH_2)_2$O-Ph
C71	4-nPr-1-pipa	
C72	4-nPr-1-pipe	
C73	4-cHex-1-pipa	3-CF_3-4-HO$(CH_2)_2$O-Ph
C74	4-nPr-1-pipa	
C75	4-nPr-1-pipe	
C76	4-cHex-1-pipa	3,5-diF-4-HO$(CH_2)_2$O-Ph
C77	4-nPr-1-pipa	
C78	4-nPr-1-pipe	
C79	4-cHex-1-pipa	3,5-diCl-4-HO$(CH_2)_2$O-Ph
C80	4-nPr-1-pipa	
C81	4-nPr-1-pipe	

[0089]

[Table 14]

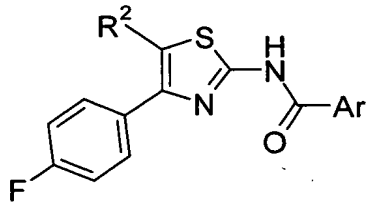


No	R^2	Ar
C82	4-cHex-1-pipa	3-Cl-5-F-4-HO$(CH_2)_2$O-Ph
C83	4-nPr-1-pipa	
C84	4-nPr-1-pipe	
C85	4-cHex-1-pipa	3-F-4-MeO$(CH_2)_2$O-Ph
C86	4-nPr-1-pipa	
C87	4-nPr-1-pipe	
C88	4-cHex-1-pipa	3-Cl-4-MeO$(CH_2)_2$O-Ph

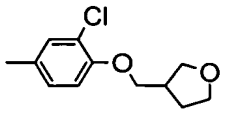
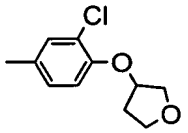
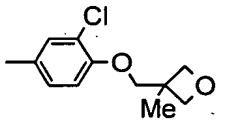
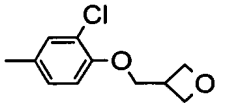
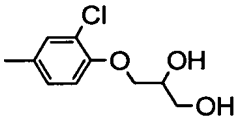
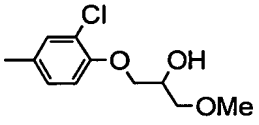
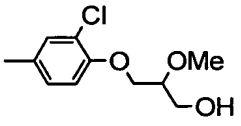
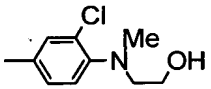
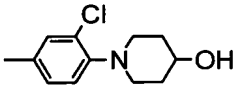
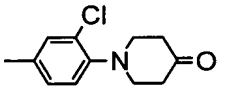
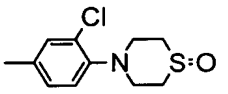
C89	4-nPr-1-pipa	
C90	4-nPr-1-pipe	
C91	4-cHex-1-pipa	3-Br-4-MeO$(CH_2)_2$O-Ph
C92	4-nPr-1-pipa	
C93	4-nPr-1-pipe	
C94	4-cHex-1-pipa	3-Me-4-MeO$(CH_2)_2$O-Ph
C95	4-nPr-1-pipa	
C96	4-nPr-1-pipe	
C97	4-cHex-1-pipa	3-CF3-4-MeO$(CH_2)_2$O-Ph
C98	4-nPr-1-pipa	
C99	4-nPr-1-pipe	
C100	4-cHex-1-pipa	3-Cl-4-HO$(CH_2)_3$O-Ph
C101	4-nPr-1-pipa	
C102	4-nPr-1-pipe	
C103	4-cHex-1-pipa	3-Cl-4-MeO$(CH_2)_3$O-Ph
C104	4-nPr-1-pipa	
C105	4-nPr-1-pipe	
C106	4-cHex-1-pipa	
C107	4-nPr-1-pipa	
C108	4-nPr-1-pipe	
C109	4-cHex-1-pipa	
C110	4-nPr-1-pipa	
C111	4-nPr-1-pipe	
C112	4-cHex-1-pipa	
C113	4-nPr-1-pipa	
C114	4-nPr-1-pipe	
C115	4-cHex-1-pipa	
C116	4-nPr-1-pipa	
C117	4-nPr-1-pipe	
C118	4-cHex-1-pipa	
C119	4-nPr-1-pipa	
C120	4-nPr-1-pipe	

[0090]

[Table 15]

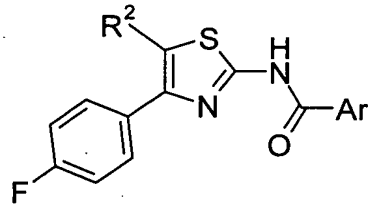


No	R^2	Ar
D1	4-cHex-1-pipa	

D2	4-nPr-1-pipa	
D3	4-nPr-1-pipe	
D4	4-cHex-1-pipa	
D5	4-nPr-1-pipa	
D6	4-nPr-1-pipe	
D7	4-cHex-1-pipa	
D8	4-nPr-1-pipa	
D9	4-nPr-1-pipe	
D10	4-cHex-1-pipa	
D11	4-nPr-1-pipa	
D12	4-nPr-1-pipe	
D13	4-cHex-1-pipa	
D14	4-nPr-1-pipa	
D15	4-nPr-1-pipe	
D16	4-cHex-1-pipa	
D17	4-nPr-1-pipa	
D18	4-nPr-1-pipe	
D19	4-cHex-1-pipa	
D20	4-nPr-1-pipa	
D21	4-nPr-1-pipe	
D22	4-cHex-1-pipa	
D23	4-nPr-1-pipa	
D24	4-nPr-1-pipe	
D25	4-cHex-1-pipa	
D26	4-nPr-1-pipa	
D27	4-nPr-1-pipe	
D28	4-cHex-1-pipa	
D29	4-nPr-1-pipa	
D30	4-nPr-1-pipe	
D31	4-cHex-1-pipa	
D32	4-nPr-1-pipa	
D33	4-nPr-1-pipe	

[0091]

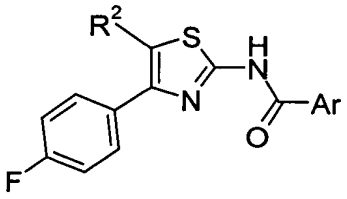
[Table 16]

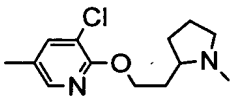
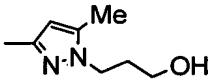
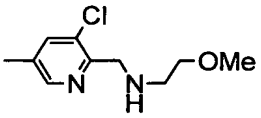
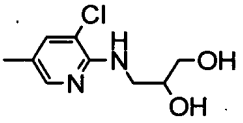
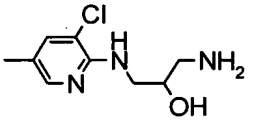


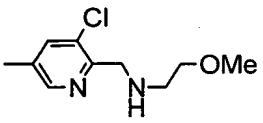
No	R^2	Ar
D34	4-cHex-1-pipa	3-Cl-4-H_2NOCCH_2O-Ph
D35	4-nPr-1-pipa	
D36	4-nPr-1-pipe	
D37	4-cHex-1-pipa	3-Cl-4-$H_2N(CH_2)_2O$-Ph
D38	4-nPr-1-pipa	
D39	4-nPr-1-pipe	
D40	4-cHex-1-pipa	5-Cl-6-$HO(CH_2)_2O$-3-Py
D41	4-nPr-1-pipa	
D42	4-nPr-1-pipe	
D43	4-cHex-1-pipa	5-Cl-6-$MeO(CH_2)_2O$-3-Py
D44	4-nPr-1-pipa	
D45	4-nPr-1-pipe	
D46	4-cHex-1-pipa	5-Cl-6-$HO(CH_2)_3O$-3-Py
D47	4-nPr-1-pipa	
D48	4-nPr-1-pipe	
D49	4-cHex-1-pipa	5-Cl-6-$MeO(CH_2)_3O$-3-Py
D50	4-nPr-1-pipa	
D51	4-nPr-1-pipe	
D52	4-cHex-1-pipa	5-Cl-6-$HO(CH_2)_3NH$-3-Py
D53	4-nPr-1-pipa	
D54	4-nPr-1-pipe	
D55	4-cHex-1-pipa	5-Cl-6-$MeO(CH_2)_3NH$-3-Py
D56	4-nPr-1-pipa	
D57	4-nPr-1-pipe	
D58	4-cHex-1-pipa	5-Cl-6-$H_2N(CH_2)_3NH$-3-Py
D59	4-nPr-1-pipa	
D60	4-nPr-1-pipe	
D61	4-cHex-1-pipa	5-Cl-6-$HO(CH_2)_2NH$-3-Py
D62	4-nPr-1-pipa	
D63	4-nPr-1-pipe	
D64	4-cHex-1-pipa	5-Cl-6-$MeO(CH_2)_2NH$-3-Py
D65	4-nPr-1-pipa	
D66	4-nPr-1-pipe	
D67	4-cHex-1-pipa	5-Cl-6-$H_2N(CH_2)_2NH$-3-Py
D68	4-nPr-1-pipa	
D69	4-nPr-1-pipe	
D70	4-cHex-1-pipa	5-Cl-6-$HO(CH_2)_2N(Me)$-3-Py
D71	4-nPr-1-pipa	
D72	4-nPr-1-pipe	
D73	4-cHex-1-pipa	5-Cl-6-$MeO(CH_2)_2N(Me)$-3-Py
D74	4-nPr-1-pipa	
D75	4-nPr-1-pipe	

[0092]

[Table 17]

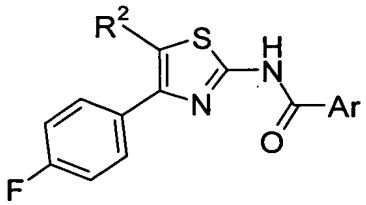


No	R^2	Ar
D76	4-cHex-1-pipa	5-Cl-6-HO$(CH_2)_3$N(Me)-3-Py
D77	4-nPr-1-pipa	
D78	4-nPr-1-pipe	
D79	4-cHex-1-pipa	5-Cl-6-MeO$(CH_2)_3$N(Me)-3-Py
D80	4-nPr-1-pipa	
D81	4-nPr-1-pipe	
D82	4-cHex-1-pipa	2-HO$(CH_2)_2$O-4-Py
D83	4-nPr-1-pipa	
D84	4-nPr-1-pipe	
D85	4-cHex-1-pipa	2-MeO$(CH_2)_2$O-4-Py
D86	4-nPr-1-pipa	
D87	4-nPr-1-pipe	
D88	4-cHex-1-pipa	
D89	4-nPr-1-pipa	
D90	4-nPr-1-pipe	
D91	4-cHex-1-pipa	
D92	4-nPr-1-pipa	
D93	4-nPr-1-pipe	
D94	4-cHex-1-pipa	
D95	4-nPr-1-pipa	
D96	4-nPr-1-pipe	
D97	4-cHex-1-pipa	5-Cl-6-HOCH(Me)CH_2NH-3-Py
D98	4-nPr-1-pipa	
D99	4-nPr-1-pipe	
D100	4-cHex-1-pipa	
D101	4-nPr-1-pipa	
D102	4-nPr-1-pipe	
D103	4-cHex-1-pipa	
D104	4-nPr-1-pipa	
D105	4-nPr-1-pipe	
D106	4-cHex-1-pipa	
D107	4-nPr-1-pipa	

D108	4-nPr-1-pipe	
D109	4-cHex-1-pipa	5-Cl-6-HOCH(Me)CH_2NH-3-Py
D110	4-nPr-1-pipa	
D111	4-nPr-1-pipe	
D112	4-cHex-1-pipa	5-Cl-6-HOCH(Me)CH_2NH-3-Py
D113	4-nPr-1-pipa	
D114	4-nPr-1-pipe	

[0093]

[Table 18]

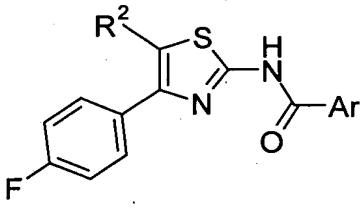


No	R^2	Ar
E1	4-cHex-1-pipa	5-Cl-6-$(HOCH_2CH_2)_2N$-3-Py
E2	4-nPr-1-pipa	
E3	4-nPr-1-pipe	
E4	4-cHex-1-pipa	5-Cl-6-(4-HO-cHex)NH-3-Py
E5	4-nPr-1-pipa	
E6	4-nPr-1-pipe	
E7	4-cHex-1-pipa	5-Cl-6-(3-HO-cHex)NH-3-Py
E8	4-nPr-1-pipa	
E9	4-nPr-1-pipe	
E10	4-cHex-1-pipa	5-Cl-6-(2-HO-cHex)NH-3-Py
E11	4-nPr-1-pipa	
E12	4-nPr-1-pipe	
E13	4-cHex-1-pipa	5-Cl-6-(4-HO-1-pipe)-3-Py
E14	4-nPr-1-pipa	
E15	4-nPr-1-pipe	
E16	4-cHex-1-pipa	5-Cl-6-(3-HO-1-pipe)-3-Py
E17	4-nPr-1-pipa	
E18	4-nPr-1-pipe	
E19	4-cHex-1-pipa	5-Cl-6-(4-$HOCH_2$-1-pipe)-3-Py
E20	4-nPr-1-pipa	
E21	4-nPr-1-pipe	
E22	4-cHex-1-pipa	5-Cl-6-(3-$HOCH_2$-1-pipe)-3-Py
E23	4-nPr-1-pipa	
E24	4-nPr-1-pipe	
E25	4-cHex-1-pipa	5-Cl-6-(2-$HOCH_2CH_2$-1-pipe)-3-Py
E26	4-nPr-1-pipa	
E27	4-nPr-1-pipe	
E28	4-cHex-1-pipa	5-Cl-6-(4-benzylamino-1-pipe)-3-Py
E29	4-nPr-1-pipa	
E30	4-nPr-1-pipe	

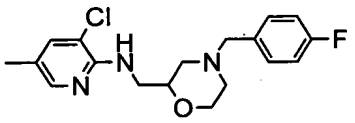
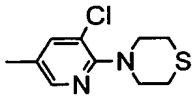
E31	4-cHex-1-pipa	5-Cl-6-(4-MeO-1-pipe)-3-Py
E32	4-nPr-1-pipa	
E33	4-nPr-1-pipe	
E34	4-cHex-1-pipa	5-Cl-6-(4-F-1-pipe)-3-Py
E35	4-nPr-1-pipa	
E36	4-nPr-1-pipe	
E37	4-cHex-1-pipa	5-Cl-6-(4-EtO_2C-1-pipe)-3-Py
E38	4-nPr-1-pipa	
E39	4-nPr-1-pipe	
E40	4-cHex-1-pipa	5-Cl-6-(4-H_2NOC-1-pipe)-3-Py
E41	4-nPr-1-pipa	
E42	4-nPr-1-pipe	

[0094]

[Table 19]

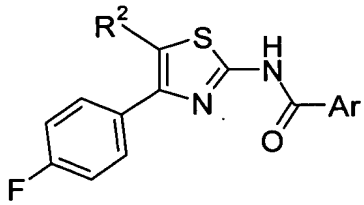


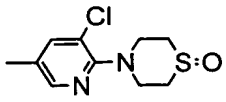
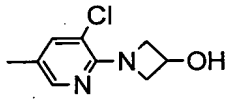
No	R^2	Ar
E43	4-cHex-1-pipa	5-Cl-6-(4-HO_2C-1-pipe)-3-Py
E44	4-nPr-1-pipa	
E45	4-nPr-1-pipe	
E46	4-cHex-1-pipa	5-Cl-6-EtO_2CCH_2NH-3-Py
E47	4-nPr-1-pipa	
E48	4-nPr-1-pipe	
E49	4-cHex-1-pipa	5-Cl-6-H_2NOCCH_2NH-3-Py
E50	4-nPr-1-pipa	
E51	4-nPr-1-pipe	
E52	4-cHex-1-pipa	5-Cl-6-HO_2CCH_2NH-3-Py
E53	4-nPr-1-pipa	
E54	4-nPr-1-pipe	
E55	4-cHex-1-pipa	5-Cl-6-(1-pipa)-3-Py
E56	4-nPr-1-pipa	
E57	4-nPr-1-pipe	
E58	4-cHex-1-pipa	5-Cl-6-(4-$MeOCH_2CH_2$-1-pipa)-3-Py
E59	4-nPr-1-pipa	
E60	4-nPr-1-pipe	
E61	4-cHex-1-pipa	5-Cl-6-(4-$HOCH_2CH_2$-1-pipa)-3-Py

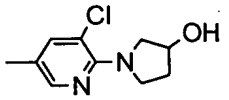
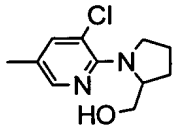
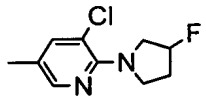
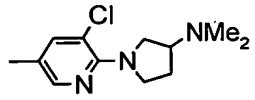
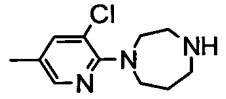
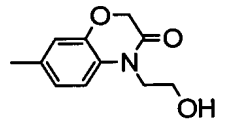
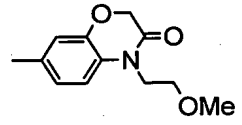
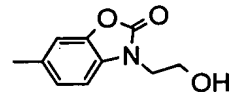
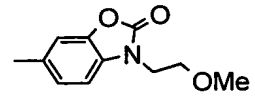
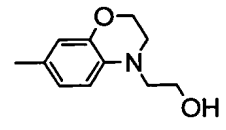
E62	4-nPr-1-pipa	
E63	4-nPr-1-pipe	
E64	4-cHex-1-pipa	5-Cl-6-(3-$HOCH_2$-4-Me-1-pipa)-3-Py
E65	4-nPr-1-pipa	
E66	4-nPr-1-pipe	
E67	4-cHex-1-pipa	5-Cl-6-(3-oxo-1-pipa)-3-Py
E68	4-nPr-1-pipa	
E69	4-nPr-1-pipe	
E70	4-cHex-1-pipa	5-Cl-6-Mor-3-Py
E71	4-nPr-1-pipa	
E72	4-nPr-1-pipe	
E73	4-cHex-1-pipa	5-Cl-6-(2-$HOCH_2$-Mor)-3-Py
E74	4-nPr-1-pipa	
E75	4-nPr-1-pipe	
E76	4-cHex-1-pipa	
E77	4-nPr-1-pipa	
E78	4-nPr-1-pipe	
E79	4-cHex-1-pipa	
E80	4-nPr-1-pipa	
E81	4-nPr-1-pipe	

[0095]

[Table 20]

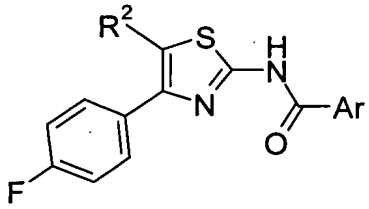


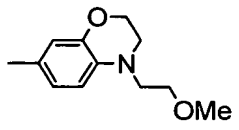
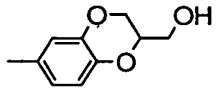
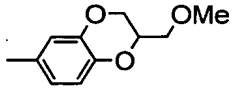
No	R^2	Ar
E82	4-cHex-1-pipa	
E83	4-nPr-1-pipa	
E84	4-nPr-1-pipe	
E85	4-cHex-1-pipa	
E86	4-nPr-1-pipa	
E87	4-nPr-1-pipe	
E88	4-cHex-1-pipa	

E89	4-nPr-1-pipa	
E90	4-nPr-1-pipe	
E91	4-cHex-1-pipa	
E92	4-nPr-1-pipa	
E93	4-nPr-1-pipe	
E94	4-cHex-1-pipa	
E95	4-nPr-1-pipa	
E96	4-nPr-1-pipe	
E97	4-cHex-1-pipa	
E98	4-nPr-1-pipa	
E99	4-nPr-1-pipe	
E100	4-cHex-1-pipa	
E101	4-nPr-1-pipa	
E102	4-nPr-1-pipe	
E103	4-cHex-1-pipa	
E104	4-nPr-1-pipa	
E105	4-nPr-1-pipe	
E106	4-cHex-1-pipa	
E107	4-nPr-1-pipa	
E108	4-nPr-1-pipe	
E109	4-cHex-1-pipa	
E110	4-nPr-1-pipa	
E111	4-nPr-1-pipe	
E112	4-cHex-1-pipa	
E113	4-nPr-1-pipa	
E114	4-nPr-1-pipe	
E115	4-cHex-1-pipa	
E116	4-nPr-1-pipa	
E117	4-nPr-1-pipe	

[0096]

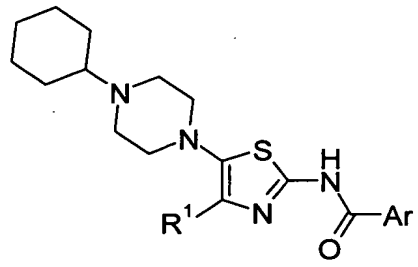
[Table 21]



No	R^2	Ar
F1	4-cHex-1-pipa	
F2	4-nPr-1-pipa	
F3	4-nPr-1-pipe	
F4	4-cHex-1-pipa	
F5	4-nPr-1-pipa	
F6	4-nPr-1-pipe	
F7	4-cHex-1-pipa	
F8	4-nPr-1-pipa	
F9	4-nPr-1-pipe	

[0097]

[Table 22]



No	R^1	Ar
G1	4-Py	3-chloro-4-(2-hydroxyethoxy)phenyl
G2	3-Py	
G3	2-Py	
G4	4-Py	5-chloro-6-(3-hydroxypropylamino)-3-pyridyl
G5	3-Py	
G6	2-Py	
G7	4-Py	quinolin-6-yl
G8	3-Py	
G9	2-Py	

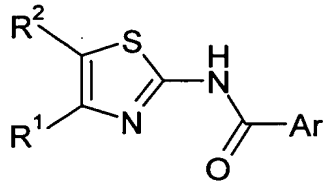
[Designation of the Document] Abstract

[Problem] To provide excellent therapeutic agent for thrombocytopenia

[Means for Dissolution]

A 2-acylaminothiazole derivative represented by the general Formula (I) and a pharmaceutically acceptable salt thereof.

[Chemical Formula]



(I)

(wherein, Ar is optionally substituted aryl, optionally substituted monocyclic aromatic heterocycle, optionally substituted bicyclic condensed heterocycle, R^1 is optionally substituted aryl, optionally substituted pyridyl, R^2 is cyclic amino such as optionally substituted piperazine, piperidine, and the like, and linear amino.)

[Selected Drawing] No